From THE DEPARTMENT OF GLOBAL HEALTH
Karolinska Institutet, Stockholm, Sweden

COST EFFECTIVENESS OF LATENT TUBERCULOSIS SCREENING AMONG ASYLUM SEEKERS IN STOCKHOLM

Jad Shedrawy

Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-7831-978-7
Cover illustration: by Faris Halteh

Cost effectiveness of latent tuberculosis screening among asylum seekers in Stockholm

THESIS FOR DOCTORAL DEGREE (Ph.D)

By

Jad Shedrawy

The thesis will be defended in public at Inghelesalen, Widerströmska Huset, Karolinska Institutet, Sweden. Date: Friday the 5th of February 2021.

Principal Supervisor:
Knut Lönnroth
Karolinska Institutet
Department of Global Public Health

Co-supervisor(s):
Asli Kulane
Karolinska Institutet
Department of Global Public Health

Andrew Siroka
World Health Organization
Department of Health systems, Governance and Financing

Charlotte Deogan
Karolinska Institutet
Department of Global Public Health

Opponent:
Fredrik Norström
Umeå University
Department of Epidemiology and Global Health

Examination Board:
Peter Lindgren
Karolinska Institutet
Department of Learning, Informatics, Management and Ethics

Malin Inghammar
Lund University
Department of Infectious Medicine (BMC)

Bernadette Kumar
Empower School of Health

“To those who crossed oceans for the hope of a decent life,
maybe one day you won’t be seen as a burden anymore,
maybe one day we won’t need to write for your rights anymore.”

POPULAR SCIENCE SUMMARY OF THE THESIS

Tuberculosis (TB) is an infectious disease that most commonly affects the lungs. In Sweden, the vast majority of TB cases are among migrants who have acquired TB infection in their home country or during the migration process. They may carry a dormant form of TB, so-called latent tuberculosis infection (LTBI), which can later activate to infectious TB disease. This activation can be hindered through screening and treatment of LTBI. Therefore, one of the key interventions to control TB in Sweden is screening and treating LTBI. Newly arrived migrants are offered a health examination where they get tested for infectious diseases including TB and LTBI. Following a positive LTBI test, individuals can be referred to a TB clinic for follow-up and potential prescription of LTBI treatment.

This thesis is composed of 5 articles that explore the experiences of newly arrived migrants with the health examination, LTBI/TB diagnosis and treatment and assess the cost effectiveness of the LTBI screening strategy in Stockholm Region.

As the overall aim of the thesis was to assess the cost effectiveness of LTBI screening, Study I was a literature review that looked at the methodology of economic modelling in this field and developed an analytical framework, setting the stage to perform the cost-effectiveness analysis in Study V. The economic modelling study showed that screening was cost effective among individuals in the age group 13 to 19, while it was less cost effective among younger children mainly because LTBI was not prevalent in this group. For the age group 20 to 34, screening was also less cost effective compared to the adolescent group because patients, even when screened positive for LTBI, were rarely referred to the TB clinic to start treatment. However, if more patients would start treatment, screening is expected to be cost effective in this age group too. Finally, screening was not cost effective for people above the age of 34.

Study II explored the experiences of newly arrived migrants with health examination through conducting interviews with them. The interviewed migrants expressed positive attitude toward the health examination but perceived the examination as too much focused on infectious disease control rather than an examination that focuses on all their health needs. In addition, they expressed a need for better information about the Swedish healthcare system during the examination.

Study III and IV relied on interviews and surveys that included instrument to measure the health-related quality of life of patients. The results showed that TB patients are affected in terms of physical and mental health. While LTBI patients did not have a compromised quality of life, there was a large proportion of them who reported mental health concerns, although these concerns can be related to their asylum-seeking process. Nevertheless, several expressed fear of infecting others and about the burden of TB on them. Therefore, addressing fears and misinformation through counseling might be beneficial in this group.

Altogether, these results emphasize the need for a better communication system between migrants and healthcare professionals to address concerns and fears during health examination, LTBI /TB diagnosis and treatment. Due to ethical and economic reasons, LTBI screening should only be performed for asylum seekers who are potentially eligible for treatment.

ABSTRACT

Introduction The burden of tuberculosis (TB) in Sweden is concentrated among migrants from high TB incidence countries. The incident cases in Sweden arise mainly through reactivation of a latent tuberculosis infection (LTBI) acquired in the home country or during transit. Progression from LTBI to active TB disease can be prevented through treatment with anti-tubercular medicines. LTBI screening is therefore offered for asylum seekers and refugees in Sweden as part of a voluntary health examination (HE). Little is known about their experiences of LTBI screening and treatment. In addition, there has been no previous evaluation of the cost-effectiveness of the current LTBI screening policy in Stockholm or Sweden.

Aims The overarching aim of this thesis was to determine the cost-effectiveness of the current strategy of screening for LTBI among asylum seekers in Stockholm. This aim was achieved through the following specific objectives: 1) to assess the methodology of previously published economic models of LTBI screening and to develop an analytical framework, 2) to understand the experiences of asylum seekers with HE, 3) to quantify health-related quality of life (HRQoL) of LTBI patients and to explore the factors influencing it, 4) to quantify the HRQoL of TB patients, and 5) to assess the cost effectiveness of LTBI screening through an economic model.

Methods A qualitative study was designed to explore the experiences of asylum seekers with HE; semi-structured interviews were conducted based on an interview guide. For the HRQoL studies, a HRQoL instrument, EQ-5D, and a mental health screening instrument, RHS-15, were used. For the LTBI patients, a mixed-method design was used, in which a cross-sectional survey using the EQ-5D and RHS-15 instruments was combined with qualitative interviews of a subgroup. For the TB patients, a longitudinal study design was used in which a cohort filled the EQ-5D instrument at the beginning and the end of treatment. A literature review was performed to assess the methodology of published economic modelling studies of LTBI screening. Through this review a framework was developed guiding the development of an economic model (a Markov model) to assess the cost effectiveness of the current LTBI screening in Stockholm compared to a hypothetical scenario of no screening. The analysis adopted the societal perspective, and results were presented in term of incremental cost-effectiveness ratios (ICERs); taking 500 000 SEK/QALY as a cost-effectiveness threshold.

Results The HE was perceived as available by asylum seekers, with no serious physical or financial accessibility problems. They felt respected and trusted by the healthcare workers. However, information about the Swedish healthcare system was perceived to be incomplete and the HE was seen as non-responsive to their individual needs with main focus on infectious diseases. Among LTBI patients, 38% screened positive for mental health concerns using RHS-15, and 28% scored problems on mental health dimension of EQ-5D. These patients expressed fear of being contagious to others, an ambiguous threat of a vague diagnosis and future uncertainties about developing TB disease. However, LTBI patients had no overall HRQoL decrement. TB patients had a HRQoL utility score of 0,72 at the beginning of treatment, which improved significantly by the end of the treatment to 0,84. The cost effectiveness results showed that ICER is the lowest among the age group 13 to 19 at 303 881 SEK/QALY, which was the only ICER below the 500 000 SEK/QALY threshold.

Discussion Asylum seekers had a generally positive attitude towards HE, including TB and LTBI screening, but also emphasized the need to broaden the focus on all health needs rather than solely focusing on infectious diseases. LTBI patients might have a compromised mental health partly linked to fear of TB disease. Therefore, it can be beneficial to address these concerns as part of LTBI management. TB patients had a compromised HRQoL and a decrement of 0,28 for TB patients is recommended to be used in economic evaluations. LTBI screening among asylum seekers in Stockholm is cost effective in the age group 13 to 19 while it is moderately cost-effective in the age groups 0 to 12 and 20 to 34 years. The latter is mainly due to the restrictive practices of offering treatment for persons over the age of 20 years.

Conclusions Health examination is an acceptable, accessible health service. However, its quality can be improved by broadening the focus beyond infectious disease control. An LTBI diagnosis can be misunderstood as active TB and linked to stigma. The cost-effectiveness analysis showed that screening is cost effective only when preventive treatment is offered. Therefore, due to ethical and economic reasons, LTBI screening should only be performed for asylum seekers who are potentially eligible for LTBI treatment.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles, referred to in the text by their Roman numerals:

I. **Shedrawy J,** Siroka A, Oxlade O, Matteelli A, Lönnroth K. Methodological considerations for economic modelling of latent tuberculosis screening in migrants. Int J Tuberc Lung Dis. 2017; 21(9): 977–989

II. **Shedrawy J,** Lönnroth K, Kulane A. Valuable but incomplete! Migrants' perspective on Health examinations in Stockholm. International Health. 2018; 10(3): 191-196.

III. **Shedrawy J,** Jansson L, Röhl I, Kulane A, Bruchfeld J, Lönnroth K. Quality of life of patients on treatment for latent tuberculosis infection: a mixed-method study in Stockholm, Sweden. Health Qual Life Outcomes. 2019;17(1):158.

IV. **Shedrawy J,** Jansson L, Bruchfeld J, Lönnroth K. Health-related quality of life among tuberculosis patient in Stockholm, Sweden. Int J Tuberc Lung Dis. 2020;24(4): 461-463.

V. **Shedrawy J,** Deogan C, Nederby Öhd J, Hergens MP, Bruchfeld J, Jonsson J, Siroka A, Lönnroth K. Cost-effectiveness of the latent tuberculosis screening program for migrants in Stockholm Region.(Submitted)

Scientific papers not included in the thesis:

Wikell A, **Shedrawy J,** Röhl I, Jonsson J, Berggren I, Buxbaum C, Lönnroth K, Bruchfeld J. Diagnostic pathways and delay among tuberculosis patients in Stockholm, Sweden: a retrospective observational study. BMC Public Health.2019;19(1):151.

Jansson L, **Shedrawy J,** Kulane A, Lönnroth K, Bruchfeld J, Popenoe R. Latent tuberculosis in pregnant women - a patient perspective. Int J Tuberc Lung Dis. 2020;24(3):310-315.

Nederby Öhd J, Hergens MP, Luksha Y, Buxbaum C, **Shedrawy J,** Jonsson J, Bruchfeld J, Lönnroth K. Assessment of the care cascade of latent tuberculosis screening and treatment of asylum seekers in Stockholm, Sweden 2015-2018 - a record linkage study. Eur Resp J. 2020.

CONTENTS

LIST OF ABBREVIATIONS

AAAQ	Availability Accessibility Acceptability Quality
ADR	Adverse Drug Reaction
BCG	Bacille Calmette–Guérin
CEA	Cost-Effectiveness Analysis
CUA	Cost-Utility Analysis
CXR	Chest X-RAY
ECDC	European Centre for Disease prevention and Control
EQ-5D	EuroQoL 5 Dimensions
EQ-5D-3L	EuroQoL 5 Dimensions 3 Levels
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
HE	Health examination
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IGRA	Interferon Gamma Release Assay
IOM	International Organization of Migration
LTBI	Latent Tuberculosis Infection
M. Tuberculosis	Mycobacterium Tuberculosis
MDR-TB	Multi-Drug Resistant Tuberculosis
PLHIV	People living with HIV
PPD	Purified Protein Derivative
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
RHS-15	Refugee Health Screener-15
SEK	Swedish Krona
SF-36	Short Form health survey with 36 items
TB	Tuberculosis
TLV	Swedish Dental and Pharmaceutical Benefits Agency
TNF	Tumor Necrosis Factor
TPT	Tuberculosis Preventive Treatment

TST	Tuberculin Skin Test
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

1.1 TUBERCULOSIS DISEASE

1.1.1 Pathogenesis

Tuberculosis (TB) is an ancient bacterial disease that has affected humans for thousands of years. It is caused by Mycobacterium tuberculosis (M. tuberculosis), a bacillus that was discovered by Dr. Robert Koch in 1882. (1) TB is an airborne communicable disease that can be transmitted by aerosols droplets through coughing, talking or sneezing. Many factors influence the probability of transmission between humans such as the infectiousness of the TB case, the duration and closeness of the contact, and the physical environment where the contact takes place. (2,3)

In the majority of cases, TB manifests as a respiratory disease affecting the lungs which is referred to as pulmonary TB. (4) Symptoms occur gradually within weeks to years after infection with a more acute onset often observed in immunocompromised and young patients. The most common symptom is persistent cough as well as triad of fever, weight loss and night sweats.(5) However, TB is multisystem disease that can affect any organ through dissemination of the M. Tuberculosis to these organs from infected lungs, which results in extrapulmonary TB.(4,6) The most common anatomic sites of extrapulmonary TB are lymph nodes. Other common sites include the pleura, the central nervous system, bones, joints, urogenital tract, skin, ect. (7) As extrapulmonary TB can have a wide variety of clinical manifestations and may mimic other diseases, its diagnosis can be challenging. (6)

As with any other infectious disease, many health-related risk factors such as diabetes, smoking, undernutrition, harmful use of alcohol are shown to affect the risk of infection, progression of the disease and treatment outcomes.(8) However co-infection with a human immunodeficiency virus (HIV) is considered the most important individual-level risk factor for developing active TB; (9) People living with HIV have a 16 to 27 times higher risk compared to the HIV-negative individuals. (10,11)

Aside of health-related risk factors, TB disease is influenced by the socio-economic status of individuals which affect the risk of exposure, susceptibility of progression, and treatment outcomes. For example, working and living conditions, including crowding and ventilation influence the risk of exposure to TB while economic constraints and poverty can limit the use of health services and treatment compliance. (8) To no surprise, studies show that areas with higher socioeconomic depravation have higher TB incidence due to higher prevalence of socially determined risk factors for exposure and infection such as crowding, poor living conditions, co-morbidities that aggravate TB and financial insecurity that hampers access to care. (12,13)

1.1.2 Treatment of active TB

Active TB is normally a curable disease. Except in cases of extensive drug resistance, antibiotic treatment can cure the disease and hence also decrease the risk of transmission to others. (5)

In order to reduce the risk of acquired drug resistance, treatment includes a combination of antibiotics administered over a period of 6 to 9 months with the following first line drugs normally forming the core of the treatment of drug-susceptible TB: isoniazid, rifampicin, ethambutol and pyrazinamide. (14) However, antimicrobial resistance is a rising challenge in TB management. M. tuberculosis can be resistant to one or more of the first-line antibiotics, which complicates pharmacotherapy especially in case of Multi-Drug Resistant TB (MDR-TB), which is defined as M. Tuberculosis being resistant to the two most important first line antitubercular drugs: isoniazid and rifampicin. MDR-TB complicates the clinical and public health management of TB considerably as second and third line drugs have to be used and these alternatives are more costly, typically associated with more severe side effects and need to be taken for a much longer time-period than the first-line treatment.(15)

Efficacy of TB treatment is high in the absence of antimicrobial resistance. However effectiveness depends on many factors that can be summarized in 4 categories: 1) patient-related factors (such as adherence to treatment, age, immunity, HIV co-infection), 2) pathogen-related factors (virulence of the organism, susceptibility of the strain), 3) care-related factors (access to high-quality healthcare, monitoring and observation of treatment) 4) treatment-related factors (antibiotic choice, dose of drugs, side effects, drug interactions.). (16) Therefore, many challenges can hinder a good prognosis and compromise the success of the therapy.

1.1.3 Latent Tuberculosis Infection

Exposure to M. tuberculosis may result in a latent form of tuberculosis infection (LTBI), a state in which the immune system of the infected person is controlling the replication of the bacillus and preventing the progression to the active symptomatic and infectious disease.(17) In clinical term, LTBI is a condition in which a specific immune response to M. tuberculosis antigens is detected in a healthy subject that shows no symptoms of active TB.

Around one fourth of the world´s population is estimated to be infected with LTBI. (18) These persons are not infectious. However, there is a lifelong risk of activation to symptomatic and infectious TB. The lifetime risk is estimated to around 5 to 10%. Most activations happen within the first 5 years and around 50% within the first 2 years. The risk then diminishes over time, but can increase at a later stage in life due to for example disease or old age that impair the immune system. (19,20)

Risk of activation is higher when the immune system is compromised for example at old age or in the presence of HIV co-infection, undernutrition, diabetes, renal failure, as well as a prolonged use of medications that weaken the immune system such as corticosteroids and anti-TNF-alpha.(21–23) In addition, some sub-populations are considered high risk groups due to their environmental and social conditions including prisoners, immigrants from high-TB incidence countries, homeless people and illicit drug users.(24) These groups are often at higher risk of both exposure (e.g. due to their living conditions) and to progression (due to high prevalence of risk factors that weaken their immune system). They might also have limited access to healthcare services which delays or hinder the TB diagnosis and treatment completion mainly due to financial constraints. (8,9,13)

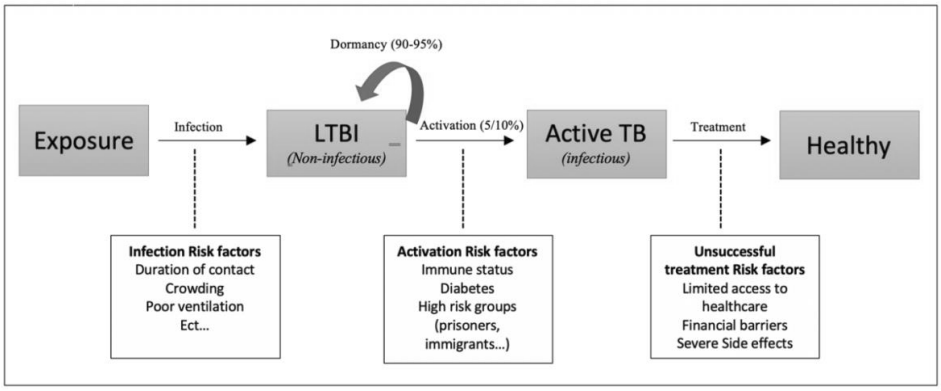


Figure 1 Schematic illustration of the LTBI exposure-infection-activation cascade along with the risk factors

1.1.4 Global burden of disease and global response

TB is the leading cause of death from a single infectious agent and one of the top 10 causes of death worldwide. In 2019, an estimated 10 million people fell sick with TB disease of which around 1.2 million died among the HIV negative population and an additional 208 000 among people living with HIV(PLHIV). These numbers have been steady in the last years showing that TB is still a huge global health concern.(9)

The burden of TB disease concentrates in low- and middle-income countries mainly in South east Asia and Africa that accounted for 44% and 25% of global TB cases in 2019, respectively. The World Health Organization (WHO) classifies countries according to the TB burden, in term of incidence rate and absolute number of cases, with 30 high-TB burden countries accounting for 87% of the worlds' TB cases. Only 8 of these countries (summarized in figure 2) contribute two third of the global cases.(9) This TB burden distribution shows the inequalities in prevention and health care delivery on a global level as 95% of morbidity and mortality occur in low- and middle-income countries where people suffer from poverty and suboptimal access to care.(5) On the other hand, most high income countries have a low burden of TB. Most of the low-TB incidence countries, meaning that TB incidence is less than 100 cases per million, are high-income countries.(9)

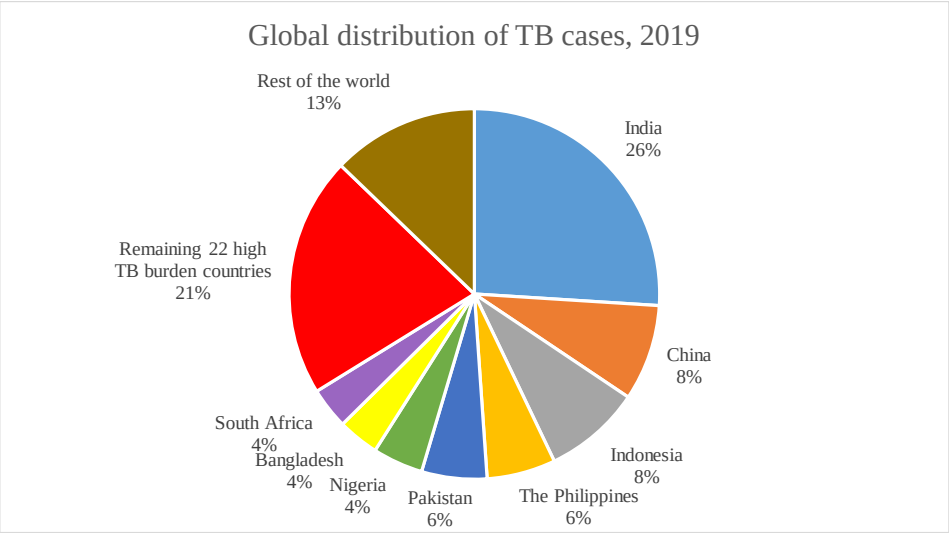


Figure 2 Global distribution of TB cases in 2019.

Information Source: global Tuberculosis Report 2010, World Health Organization, 2020
**remaining 22 high burden countries list includes: Angola, Brazil, Cambodia, Congo, Central African Republic, DPR Korea, DR Congo, Ethiopia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Papua New Guinea, Russian Federation, Sierra Leone, Thailand, the United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe*

To address the global burden of TB and its inequalities, WHO has developed the "End TB Strategy" with the aim of reducing TB incidence rate by 90%, which is equivalent to reducing the global incidence of TB from >1 000 to <100 cases per million population by 2035. The strategy also aims to reduce TB deaths by 95% between 2015 and 2035, and to eliminate catastrophic costs for TB-affected families (defined as the total cost of TB care exceeding 20% of the annual income of the household). (25)

In order to reach these goals both high-burden and low-burden countries need to intensity their effort: In high burden settings efforts need to be broad and should focus on primary prevention as well as universal health coverage in order to achieve early detection of TB and ensuring treatment success while screening TB contacts to stop domestic transmission and manage LTBI in close contacts. (26)

On the other hand, in low-burden settings, TB concentrates almost exclusively in certain vulnerable groups such as the homeless, prisoners and migrants from high-burden countries. Although society-wide prevention and universal health coverage is obviously essential in low-incidence countries too, special targeted screening efforts play a relatively more important role in these settings where the burden is highly concentrated to certain sub-populations. TB transmission rates are usually low in low-incidence countries, and even when it occurs, transmission usually take the form of limited outbreaks within the household or sub-community around the affected individuals.(27–29) The majority of cases in low-incidence settings result from re-activation of LTBI acquired mainly abroad, especially within the migrant population. (30) Therefore, in term of prevention in low burden settings,

high priority needs to be given to LTBI screening and management, including in the form of contact investigation, outbreak management, and screening of specific population risk groups. (26) The different strategies of prevention are detailed in the next section.

Most of the high-income countries have a low TB burden.(23) However, meeting the End TB strategy goals would require actions not only in the high-incidence countries but also in the low-incidence countries so that they also reach a 90% reduction in incidence, leading to a pre-elimination stage (< 10 cases per million) followed by the elimination phase (<1 case per million).(25)

1.1.5 Prevention of TB

WHO highlights 3 levels of essential preventive action: the primary prevention that aims to improve the overall health of the population and address societal and individual-level risk factors; secondary prevention which aims to improve health through early detection and management of disease; and tertiary prevention which is concerned with recovery and rehabilitation. (31) In term of TB prevention, actions can be taken at the primary level through addressing underlying risk factors and social determinants, as well as through vaccination, while secondary prevention can be performed through early TB and LTBI detection and management.

A) Primary prevention

1) Addressing risk factors and social determinants

The yearly number of TB cases can be reduced through addressing the health-related risk factors associated with the disease, which can include initiatives for smoking cessation, diabetes control and HIV prevention and control. (24) In addition, taking a multisectoral approach to tackle the determinants of TB infection and disease on a broader level can help in reducing the burden, e.g. through initiatives against undernutrition, bad housing quality and crowding, air pollution and most importantly poverty reduction. (32) Ending extreme poverty through social protection programs in high burden countries can result in substantial reduction in global TB burden and cross-sectional social protection approaches are important complements to health interventions in order to achieved the End TB targets. (33)

2) BCG vaccination

The Bacille Calmette–Guérin (BCG) vaccine is the only licensed vaccine that is used worldwide to prevent TB. It has been used since 1921. (34) It has been proven to protect against severe forms of tuberculosis in children. Therefore, WHO recommends BCG as part of the childhood immunization programs in high burden countries while limiting the recommendation to high-risk groups in low-burden settings. (24,34) However, despite very high BCG vaccination rates in most high burden countries the incidence rates remain high. (35) This reflects the low BCG efficacy in terms of impact on risk of falling ill with TB during adulthood. There is a pipeline of new vaccine candidates, but as yet no licensed vaccine that can effectively protect against TB disease before or after exposure to infection in adults. (24,35)

B) Secondary prevention

1) Early detection and treatment of active TB

A cornerstone in preventing TB is the early detection and effective treatment for patients with active TB. In doing so, the clinical outcome will be improved and transmission of TB to others will decrease, leading to less TB transmission and cases. (36) As transmission is mainly driven by people with TB being undiagnosed or diagnosed after a long delay, which leads to a long period of infectiousness, effort are needed both to improve equitable access to care, as well as to detect cases through screening programs targeting high risk groups and hyperendemic communities, while ensuring that screening and detection is followed by prompt treatment initiation and efforts to enhance adherence and completion.(25,36–38)

2) LTBI management

Currently, preventing TB activation in latently infected persons cannot be effectively achieved through vaccination. However, prevention is possible through prevention of LTBI prophylaxis, referred to as TB preventive treatment (TPT), or chemoprophylaxis, which is the only medical intervention available at this point to prevent progression to active TB disease in individuals already infected with M. Tuberculosis. (24) The screening, treatment and management guidelines of LTBI will be discussed in the next chapter.

1.2 LTBI MANAGEMENT

1.2.1 Screening tools

The tuberculin skin test (TST) was for a long time the only test for LTBI diagnosis. It works by identifying an immune response to tuberculin, a purified protein derivative (PPD) of M. tuberculosis. The individual gets an injection of PPD at the first visit then has to return after 48 to 72 hours to measure the TST reaction on the skin. This test has some disadvantages such as the need for a return visit which might be problematic for hard-to-reach populations. Moreover, it has a low specificity especially in populations with high coverage of BCG vaccination as the PPD itself has a mixture of antigens that are shared by M.tuberculosis, M. bovis, and BCG.(39) In addition, the TST interpretation may be affected by the PPD dose and/or by operator variability in term of inoculation and reading of the results and in general there is no one cut-off that is considered to be related to positive diagnosis and the cut-off recommendations differ depending on the age and risk factors.(40,41)

In the early 2000s, another family of LTBI tests was introduced: interferon gamma release assays (IGRAs). These blood tests rely on detecting interferon gamma produced by the T cells as a result of the exposure to M. tuberculosis antigen. (39,40) Two IGRAs are currently commercially available, the QuantiFERON®-TB Gold Plus (QFT-Plus) (Qiagen, Hilden, Germany) and the T-SPOT®.TB test (Oxford Immunotec, United Kingdom). IGRAs are more expensive compared to TST. However, it is performed in one visit while TST needs two visits as well as training in reading and interpreting the results.

Both IGRA and TST tests have limitations, as they cannot differentiate between LTBI and TB, they don’t differentiate between re-activation and re-reinfection and they cannot

differentiate who, among those with a positive test, have a higher risk of progression to TB.(42) Moreover, test accuracy is compromised in immunocompromised patients(43–45). IGRA has shown higher specificity than TST. However, there is no gold standard method for LTBI diagnosis and either of the tests is recommended by WHO depending on the availability, affordability and the practicality of testing in a specific setting.(17,46) Chest X-ray (CXR) is not considered as an LTBI diagnosis tool, however CXR along with symptom screening are recommended to rule out active TB when IGRA or TST are positive .(17)

1.2.2 Tuberculosis Preventive Treatment

WHO recommends one of the following regimens for LTBI treatment: 6 months of isoniazid monotherapy, 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone.(46) The efficacy of these regimens vary in the literature from 60 to 90%.(47)

Common adverse drug reactions (ADR) of isoniazid treatment are dizziness, fatigue as well as dermatological and gastrointestinal side effects. However, the most concerning ADR is hepatotoxicity, shown by an elevation of liver enzymes which can vary from being asymptomatic to causing liver injuries, and in cases patients experience a fulminant liver failure requiring a liver transplant or even causing death. (48,49) following a high elevation of liver enzymes and serious ADR, TB treatment is discontinued, and the risk is shown to be higher in older age groups. (50)

Rifampicin-based regimens have lower toxicity including hepatotoxicity compared to isoniazid, however they share similar profile of ADR including discoloration of body fluids and serious drug interactions with other medications that patients might be using such as HIV medications and anticoagulants.(51,52) Therefore the WHO guidelines recommend chemoprophylaxis depending on age and risk factors, so that the benefits of the treatment would outweigh the risk of ADR. Even when risk is deemed low and chemoprophylaxis is initiated the guidelines emphasizes the need to monitor ADR. (46,53)

1.2.3 Screening strategies

Apart from the choice of diagnostic tool, the question of who to screen for LTBI is also critical as not all individuals infected with LTBI will activate to TB. The average lifetime risk of progression is between 5% and 10%, with the highest risk soon after infection. However, the risk varies significantly depending on risk profile of the patient. Therefore, using existing tools for screening and treating individuals who are at low risk of activation is likely to be inefficient, costly and comes with the risk of ADR of TPT that might be higher than the benefits. The WHO guidelines strongly recommend screening and treating selective groups at highest risk of LTBI infection and progression to active disease so that the benefits clearly outweigh the risks. According to WHO, these risk groups are mainly people who are household contacts of a TB patient, immunosuppressed patients such as PLHIV, patients initiating anti-Tumor Necrosis Factor (anti-TNF) treatment, and patients on dialysis. (10)

WHO latest guidelines thus recommend TPT for people living with HIV, household contacts of confirmed TB cases and for groups with listed clinical risk factor.(9) In addition, a recent review by the European Centre for Disease prevention and Control (ECDC) about LTBI in

the European region identified key populations that might be eligible for LTBI screening including prisoners, homeless people and migrants from high incidence countries. However, both WHO and ECDC acknowledged the current lack of evidence about which strategies to be adopted and which key populations to target in order to yield the highest impact at lowest risk with the resources available; (54) In other words, it is a question of effectiveness and cost effectiveness of LTBI screening strategies that has to be answered in each specific setting as for example a recommendation for screening migrants would depend on their country of origin, age and risk profile as will be elaborated on in the next chapter about migration and TB.

1.3 MIGRATION AND TB

1.3.1 Migration concepts

Migration is defined by the International Organization of Migration (IOM) as the movement of individual(s) from their usual place of residence, whether within the same state or across international boarder. In the latter case the person is referred to as an immigrant.(55) A foreign-born is defined as a person who has ever migrated from their country of birth to the current country of residence.(56)

Migration for purpose of studies or work opportunities abroad are among the common motivations for migration. Another common category is forced migration happening when people migrate due to poverty, violence or war. (57) Many of these migrants seek asylum in order to gain the legal status of refugee, which is defined by the United Nation(58) as "someone who has been forced to flee his or her country because of persecution, war or violence and has a well-founded fear of persecution for reasons of race, religion, nationality, political opinion or membership in a particular social group". An asylum seeker is a person who files for a refugee status in the host country asking for the right to be recognized as a refugee and receive legal protection and material assistance.(58) Therefore, an asylum seeker is an individual who is seeking international protection, even though the person might not be ultimately recognized as a refugees. These legal differences are important to highlight as laws, rights and legislations may differ according to the legal status of the individual in a certain host nation.(55)

The current trend of migration is mainly from low-income countries to high-income countries. Taking the European region as an example, over 82 million immigrants lived in the continent in 2019, a 10 % increase compared to the figures of 2015 when the arrival of refugees via the Mediterranean route led to a huge pressure on the asylum seeking process in the EU and affected the functioning of the Schengen area as border checks were implemented between many member states. (57,59) Since then, immigration continues to be a political issue in Europe with attitudes toward immigration remaining polarized, which affect the policies of integration, access to essential services including healthcare as well as the physical, mental and social well-being on immigrants across the continent.(57,60)

1.3.2 Impact of migration on TB globally

Migration can affect TB epidemiology especially in high-income/low-incidence countries that receive migrants from low-income/high-incidence countries. These migrants face increased risk of TB exposure, poor treatment outcome and higher risk of antimicrobial resistance, all exacerbated by many factors at pre-departure, during transit and after arrival in the host country. (61,62)

In their home country, their health status, access to care and possible experiences of conflicts or disasters play a major role in their pre-departure health and TB risk exposure, especially since many of the migrants are from high-TB incidence countries. (61)

Especially relevant in cases of forced migration, individuals can be at increased risk of TB due to the transit conditions and the diversity of groups moving together in similar pathways, often under unsafe and overcrowded conditions. Therefore, even migrants from low- or medium-incidence countries might be at high risk of TB exposure due to contact with other migrants along the migration trajectory. (61)

Finally, when arriving and settling in the host country many factors shape the risk of TB disease and treatment-seeking behaviors such as legal status of the migrant, the knowledge about the disease and its symptoms, the access to healthcare and screening programs, the working and living conditions, in addition to cultural and language barriers that might influence any screening or treatment outcomes. (61)

In general, studies have linked the high-TB burden in migrant population mainly to the activation of LTBI acquired in home country or in transit before arriving to the host country. The other mechanism of TB disease can be through acquiring the infection post-arrival through local transmission, which has however been shown to be low in low-incidence countries also among migrants.(28,63–65)

1.3.3 Migrants and TB/LTBI screening in low-incidence countries in Europe and elsewhere

Based on what has been discussed above, it is no surprise that most of the TB burden in European countries is concentrated among foreign-born populations and migrants. In these mostly low-TB incidence countries, the TB rates continue to decrease in native populations while this decrease is slower in migrant populations and the proportion of foreign born among TB patients is therefore increasing. (66,67) in 2015, the proportion of foreign-born among TB cases was more than 50% in the majority of the low-incidence countries (20 out of 30) , and this proportion exceeded 80% in several countries such as Cyprus, Iceland, Norway and Sweden, which shows that TB burden in these countries is heavily linked to migration.(66)

In its report “tuberculosis surveillance and monitoring in Europe 2020”, the ECDC highlights that despite the decrease in TB incidence, the burden of TB in the European region is still a major public health concern that should not be underestimated especially since it affects mainly vulnerable group such as migrants. (68) Most countries of the European Union have a national TB control plan and 80% of these countries report that reaching vulnerable

populations is a priority action, including asylum seekers, refugees and undocumented migrants.(69)

A WHO framework for TB elimination in low incidence countries has been developed which highlights 8 priority areas including the need to address vulnerable and hard-to-reach groups with emphasis on migration and cross-border issues including LTBI and TB screening and treatment for these high risk groups, optimize prevention and care of resistant TB and screening for TB and LTBI in contacts and high risk groups while providing adequate treatment.(29) However, given the likely high number needed to screen and low impact of screening all migrants for TB and LTBI, and potentially high cost, indiscriminate screening is likely to not be cost effective. Therefore, most countries adopt more selective strategies mainly based on the type of migrants and TB incidence in their country of origin according to the WHO classification.(64) Due to limited evidence, neither WHO nor ECDC provide guidance on exactly which migrants potentially to target with TB or LTBI screening, e.g based on type of migrant, TB incidence in the country of origin, age or presence of other risk factors. It remains an important research question which TB or LTBI screening strategies are the most effective and cost-effective.

TB screening for migrants

Pre-migration screening of TB, for example as part of the process to apply for a visa, has been shown to reduce incidence of TB in people from high-incidence countries shortly after arrival in the host country. However, the impact on transmission in the host country of such screening is still unclear(70). Moreover, such screening may not be feasible in many cases especially among refugees and asylum seekers. There is no evidence in the literature on epidemiological impact in the host country of systematic screening for active TB among migrants at the port of arrival and in general the evidence in support of post-arrival, both in terms of effectiveness and cost-effectiveness is weak. (71,72) The main unresolved question is if systematic screening improves early diagnosis of active TB as compared with efforts to ensure that people with TB symptoms have easy access to health care services and good knowledge about when and how to seek care. Both WHO and ECDC emphasize that policies targeting TB control among migrant, especially refugees, asylum seekers and undocumented migrant must be tailored to the risk factors of these population and implemented with appropriate social and financial support.

A further limitation of screening for active TB is that only those people who have activated at the time of screening can be detected. Since most incident cases activate at some point after arrival, the majority of cases will be missed with a one-off screening soon after arrival. As the majority of TB cases in these populations result from LTBI activation, focusing on LTBI screening and treatment seems to be of a higher priority than screening for active TB, but it also comes with challenges (29,46,70,73), which is further discussed below.

LTBI screening

There is strong evidence that LTBI screening and treatment in contacts and individuals with certain co-morbidities (like immunosuppressive diseases and medications) is effective and cost-effective and it is in accordance with the recommendations of WHO.(29,72,74) However, widening screening to all migrants from high-income countries is not yet supported

by strong evidence as benefits of systematic careening and treatment might not outweigh the harm, or may not generate sufficient impact at acceptable costs. Therefore, such screening is only conditionally recommended by WHO and when done should be targeted to those with highest risk while adapting screening strategies to local TB epidemiology and availability of resources.(46,72) As discussed above, WHO and ECDC does not provide precise advice for this targeting.

Broad conditional recommendations from international expert organizations in combination with the availability of a variety of tests, risk groups and treatment options has led to a wide range of LTBI screening strategies for migrants in different host countries. Another aspect that differs among countries is the timing of the screening: while some countries do an entry screening which means screening for LTBI immediately at the entry to the new country, other countries adopt the post-entry screening as part of the access to specific services such as primary health care service, job application or the first contact with the health care services.(75)

Decisions about LTBI screening policies in Europe need ultimately be based on the local context, cost considerations as well as the TB epidemiology in the specific setting.(72) A review summarizing the policies of TB/LTBI screening in the EU countries showed a large variation of strategies between these countries with different criteria based on the type of migrants and various thresholds for TB incidence in the country of origin, age and risk factors.(76) For example in Belgium, only asylum seekers younger than 5 years old and pregnant women get screened for LTBI with TST, while in Norway all migrants younger than 15 years old and migrants between 18 and 34 coming from countries with TB incidence more than 200/100 000 get tested by IGRA. In Germany there is no official LTBI screening. (77) Sweden has another strategy for LTBI screening that will be discussed in the next chapter.

1.4 TB IN SWEDEN

1.4.1 TB epidemiology in Sweden

Sweden is a low TB incidence country that experienced a substantial decline in TB rates in the 20th century. The lowest incidence rate registered was in 2003, about 400 cases or 4.6 cases per 100 000 inhabitants (figure 3). (78) The incidence has since continued to decrease among the Swedish born (now less than 1 case per 100 000) while it has fluctuated among the foreign born following shifting immigration trends. The large influx of asylum seekers in 2015 affected the total incidence in the country, which reached a peak of >800 (8.5 per 100 000) in 2015, and thereafter TB incidence has again declined as migration diminished in line with changing migration policies. In 2019, the incidence was 4.8 cases per 100 000. Thus, the total TB incidence in Sweden has in recent decades mainly been determined by the migration flows from high incidence countries. The proportion that are foreign born has remained around 90% throughout the period (37,78). Most of the TB cases currently are individuals aged between 15 and 40 years, which is a reflection of both the global TB epidemiology and age profile of migrants from high burden countries. There is limited domestic transmission within the risk groups and even lower outside of these groups and most of the cases occur

through activation of LTBI, which is in line with evidence from other low-incidence settings,.(28,78,79)

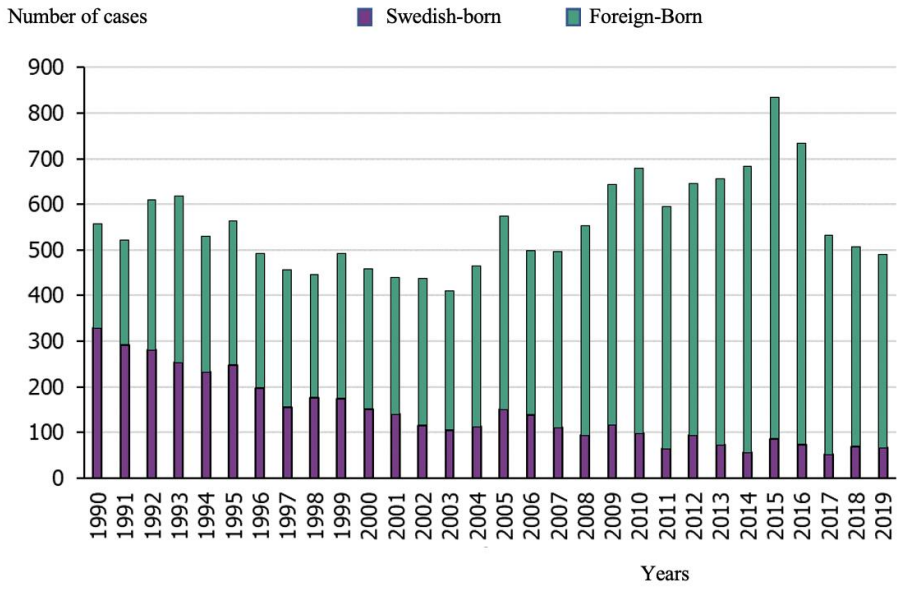


Figure 3 Number of notified TB cases in Sweden from 1990 till 2019. Source: The Public Health Agency of Sweden, 2020

1.4.2 TB and LTBI screening in Sweden

In Sweden, LTBI screening and treatment is currently recommended for four main risk groups which are presented in table 1.(80) First, contacts of a TB case are screened and followed though a mandatory contact tracing policy. Recently infected individuals are at a high risk of developing active TB and detecting it at an early stage can hinder the activation and the further spread of the infection. Another risk group are patients on immunosuppressive treatment as the impaired immunity leads to an increase risk of TB activation. This patient group includes patients starting on anti-TNF alpha inhibitors, transplant recipients, persons undergoing regular dialysis. Recommendation in Sweden, aligned with international guidelines also emphasize the need to screen PLHIV due to the high risk of co-infection with TB, therefore PLHIV is another major risk group for LTBI screening.

Table 1 LTBI screening policies for different target groups in Sweden [81]

Target group	Screening policy
TB contacts	Mandatory contact tracing
PLHIV	Screening for LTBI and TB is part of the clinical routine
Immunosuppressed patients	Screening as part of their medical care
Pregnant women from high-incidence countries	Screening pregnant women born in high-incidence countries (> 100 / 100 000), in some regions only
Asylum seekers (and other migrants eligible for health examination)	Screening for asylum seekers from high-incidence countries (> 100 / 100 000) as part of a voluntary health examination

A recent Swedish study has shown the increased risk of TB activation in connection with pregnancy, especially in the 6 months post-partum which is in line with the conclusions drawn from a similar Study in the United Kingdom (UK). (82,83) Before the new guidelines of 2020, there were no firm conclusions about the need to screen pregnant woman and only some regions in Sweden, including Stockholm, started screening pregnant women born in high-incidence countries for LTBI. However, the new recommendations highlights the need to screen this group. (81)

The largest risk group in the country that is considered for LTBI screening are recent migrants coming from high-incidence countries, many of whom can be assumed to have had contact at some point with a TB case in their home country or along the migration route. Sweden has a policy of screening migrants from countries with a TB incidence of more than 100 /100 000 as well as migrants with high risk of TB exposure (e.g in refugee camps or prisons during the migration process) with TST or IGRA. IGRA/TST screening, together with symptom screening is used as a strategy for detecting both active cases and LTBI in Sweden, while most other low-incidence countries do chest X-ray screening for all, and then some add LTBI screening with TST/IGRA. In Sweden, a chest X-ray is done after a positive IGRA test to further screen for active TB.(84,85)

The screening takes place as part of a voluntary health examination for asylum seekers (and quota refugees and some joining family members) arriving to Sweden. Thus, this screening is not offered for all types of migrants; however, the new guidelines of the public health agency of Sweden in 2020 has added a note about the need to screen also people from countries with a high TB incidence regardless of their legal status and the reason of migration. Hence, people moving for studies or work should also be considered a risk group eligible for LTBI screening, although there is as yet not specific programme or infrastructure set up for this, meaning that such screening should be integrated into general health care for this group. (81)

All asylum seekers who attend a health examination, regardless of TB incidence in the home country, are screened for TB symptoms and referred for chest X-ray if symptomatic, in order to identify active TB. Asylum seekers eligible for LTBI screening are offered screening and a positive IGRA or TST test is followed by an X-ray. A positive X-ray leads to referral to TB specialist while a negative X-ray requires the assessment of age and risk factors to decide

whether the individual should be referred to a specialist or not. This process of screening is explained in detail in one of the related articles of this thesis and summarized in a flow chart extracted from that study (figure 4). (84) The procedure and the challenges around the health examination are the focus of the next section.

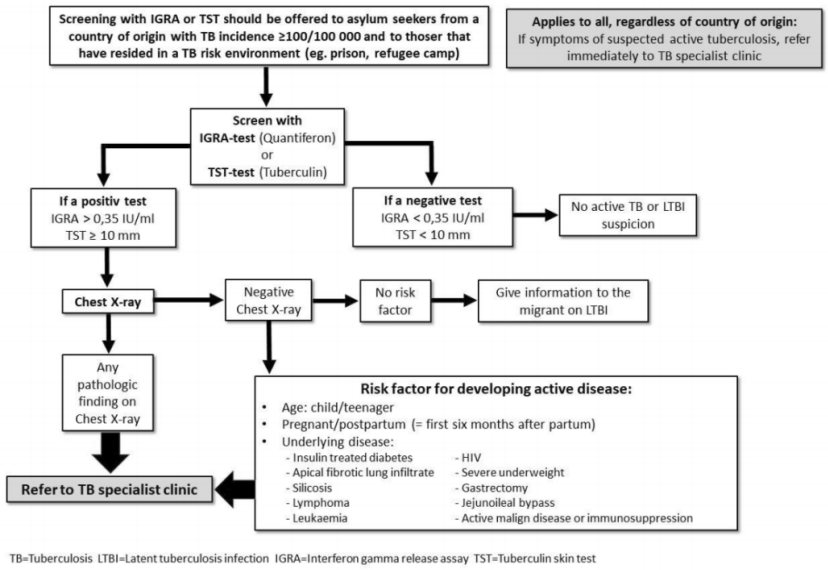


Figure 4 Flowchart of tuberculosis screening of asylum seekers in Stockholm region 2015-2018. (84)

1.4.3 Health examinations in Sweden

Asylum seekers in Sweden are entitled to necessary medical care as provided by the Swedish reception of asylum seekers' act (LMA). This care is restricted to medical and dental care that cannot be postponed, childbirth and maternal care, contraceptive advice and abortion. Asylum seekers under the age of 18 are entitled to the same health care as any citizen and the same applies to asylum seekers who have been granted a residence permit, referred to as refugees. (86)

In Sweden, all asylum seekers, as well as quota refugees and some reunified family members including all children of school age are invited to a voluntary post-arrival health examination (HE), within which TB screening is also performed.(87,88) Asylum seekers who have received refugee status are also eligible for a HE up to two years after arrival. Migrants coming for other reasons such as studies or work as well as most late-arriving relatives are not invited to a HE. The HE is offered in the region/county they are resided. (86,89)

This examination is free of charge and voluntary. Some data indicate that the uptake of this service varies between regions in Sweden due to many obstacles in the organization and the communication between healthcare, authorities and the asylum seekers. (90) Previous

research in Sweden highlighted that poor communication, lack of clarity about the purpose of this examination and the lack of information about this service contributes to the low attendance. (91–93)

1.4.4 Knowledge gaps concerning HE and LTBI screening in Sweden

Barriers for participation in the HE can be problematic for TB control because the health examination is the first contact for these migrants with the health care system and the main opportunity to screen them for TB and LTBI. Understanding migrants' experiences with the health examination procedures, content and perceived value is critical in order to improve this health service and hence improve the entry point for infectious disease control among this group. This topic has been explored qualitatively and quantitatively in different regions of Sweden and results emphasized the need to ameliorate the health examination to tackle communicable and non-communicable diseases among asylum seekers.(93–95) This topic will be discussed further in the results and discussions of this thesis.

Neither the effectiveness nor the cost effectiveness of the current screening strategy has been evaluated prior to this doctoral project, although TB and LTBI screening has been part of the HE procedures since the mid-1990s. Moreover, there have been no previous systematic monitoring of the screening coverage, screening results, proportion of those screened positive referred for further evaluation or proportion started on treatment or completing treatment. The methodology of cost effectiveness analysis will be discussed in the next chapter.

1.5 HEALTH ECONOMICS IN TB

1.5.1 Economic burden of TB

TB disease leads to economic burden on different levels: healthcare sector, individuals as well as societies, which will be discussed below.

a) TB economic burden on healthcare

Despite being a preventable disease, TB still causes a high burden on healthcare systems in term of costs and resource use, especially in low- and middle-income countries. Some governments spend large amounts on TB care and prevention while other countries cannot afford it and rely on development assistance.(24,96) The structure and performance of the health system, including service availability, health care fees and quality of care affect the health seeking behaviors of individuals, access to care and adherence to treatment.(97) Consequently, insufficient capacities of healthcare can limit the effectiveness of TB interventions and hinder the implementation of supportive programs for patients.(98)

TB economic burden is not to be neglected even in high-income, low-incidence setting. A literature review in the European region showed high costs of TB treatment across the continent (99) A costing study from the United States of America (USA), another low-incidence country, showed similar high costs attributed to hospitalizations, emergency department visits, and outpatient visits in the first year.(100) Therefore, investing in

prevention may help reduce the burden on the health systems in both high- and low-resource settings.

b) TB economic burden on individuals

TB is considered a disease of poverty, which means belonging to the poor and to vulnerable groups (including many migrants) increases the risk of infection, progression to disease, poor treatment outcomes and severe socioeconomic consequences of the disease. Falling ill with TB can accentuate a spiral of poorer health, increased medical costs, decreased income which eventually can entrench poverty. (101) In high-burden countries, TB can drive people into poverty with research showing that from 27% to 83% of these patients experience catastrophic costs and around 50% of them obliged to sell assets or take loans as a result of TB disease.(24) Out-of-pocket payments are shown to be high in resource-constrained countries, which poses a challenge for accessing care and adhering to treatment and as consequence compromising the progress toward achieving the End TB strategy goals. (96,102)

In high income countries where TB treatment is usually covered under universal health coverage schemes (funded through taxes or social insurances schemes), the out-of-pocket cost of treatment itself might not be an obstacle. (101) However, patients can still need to cover direct non-medical costs such as transportation. This out-of-pocket payment can be an economic burden especially in migrants' populations as shown by a Dutch study highlighting that out-of-pocket payment constituted 3% of the annual income of TB patients with migrant background. (103) A major concern is the income and productivity loss due to TB (discussed under the next paragraph.

c) TB economic burden on Society

Individuals spend time seeking care, being hospitalized or looking after someone else who is sick (caregivers and parents of sick children) instead of working and being productive. Therefore, TB is also associated with productivity loss that goes beyond individual economic burden to the society in general. (104,105) As with the other consequences, productivity loss is even more of an economic threat in low-income countries. For example, a cost of illness study conducted in the African region shows that the sizeable burden on the economy is mainly due to productivity loss. These results highlight the need for better prevention programs in order to decrease the economic burden of TB disease.(105) As the economic burden and the loss of productivity cannot be ignored, social protection interventions are essential to prevent or alleviate the financial risks and losses due to TB and it can contribute to better treatment adherence and clinical outcomes.(106)

According to WHO, the majority of TB patients in the European region are in the economically productive age group aged 35 to 44 years. Hence morbidity and mortality due to TB represents a loss of human capital and has a direct effect on the household economy and the well-being of the individuals. (24,107)

In sum, TB can have devastating economic consequences on individuals and societies in low- and middle-income countries. All these financial burdens are exacerbated in case of MDR-TB, where costs are shown to be very high for patients, the health care sector and

society (96,108,109). Hence, societal costs in general should not be ignored and therefore limiting the estimations for TB costs and potential savings to a healthcare perspective only seems to underestimate the actual burden and costs of TB. (104)

1.5.2 Cost-effectiveness analysis

Resources in healthcare are finite in both poor and rich countries, whether is term of infrastructure, consumables or human resources. Therefore they need to be used in the most efficient way.(110) Limited healthcare resources is the foundation of health economics, a field that is concerned with how health systems and societies allocate its resources among different alternatives and provide tools to answer the questions of what goods and services to produce, how to produce them and who shall receive them. (111)

One of the tools for health economic evaluation that is widely used in decision making is cost-effectiveness analysis (CEA).(112) It is an analysis used to compare the value of different intervention and its outcomes in term of creating better health and longer life for people or the return on investment in monetary term.(110) CEA results are usually presented in term of incremental cost-effectiveness ratio (ICER), which is a ratio with the denominator representing the health gain from an intervention and the numerator reflecting the marginal costs of that health gain. For example, if the health gain of an intervention "A" implemented in Sweden is measured as additional averted TB case then ICER would be expressed in term of additional Swedish Kronor spent per additional averted case.(110,113) As such, economic modelling is used to predict the future costs and effects of alternative interventions in order to inform policy about alternatives for investments. In addition, these models help deal with uncertainties about different parameters by performing sensitivity analysis in which assumptions can be made when data is not available or controversial. (110)

As with other diseases, management and prevention of TB can be done through different strategies across different target groups. In term of evaluating LTBI screening and treatment strategies, the many possible variations in different components such as target population, diagnostics and treatment options discussed previously is a reason for why modelling can be helpful in assessing different scenarios. At the same time the many permutations of options can impose a challenge in the cost-effectiveness modelling. In addition, literature reviews in the field have highlighted the variations in term of economic perspective, economic inputs and measured outcomes. These inconsistencies and different approaches make it difficult to reach a firm consensus about both the most appropriate modelling approach and the most cost-effective screening strategy. (114–116)

An economic evaluation is performed from a specific perspective that will determine the type of costs included in the analysis. (110) The analysis can be performed from the healthcare provider perspective including the cost paid by the healthcare system or a third-party payer. A broader societal perspective can be used to include the direct and indirect costs for patients or households, including the time lost from work while seeking treatment or participating in a health intervention. Productivity loss is an important part of the societal perspective costs, which can be related to both the opportunity cost of time lost being in care, as well as reduced labor participation due to illness, disability, stigma and discrimination. (110) The adoption of a societal perspective raises a big measurement challenge and it might be tempting to omit

items from consideration (112). However, in the case of LTBI screening, preventing an active TB case would save many hours of productivity loss associated with disability and time lost for diagnosis, treatment and follow-up. Therefore, it would be recommended to include it in the analysis, especially in Sweden where the Swedish Dental and Pharmaceutical Benefits Agency (TLV) recommendations state the preference for a societal perspective. (117)

Cost effectiveness in term of LTBI screening and management among migrants needs to heavily rely on local indicators and TB epidemiology in the specific setting. (115) One of the critical empirical data is the cascade of care of LTBI management which will be discussed in the next section.

1.5.3 Cascade of care

A screening strategy needs to define the timing of screening, the target group, the testing algorithm, the eligibility and exclusion criteria for treatment, as well as the required interventions to enhance coverage and completion of each step in the screening and treatment cascade. The first cascade step is the screening, followed by completing the medical evaluation, recommending treatment when needed, initiating and completing the treatment. The degree of completion of each cascade step influences the effectiveness and cost-effectiveness of the strategy. It is therefore important to analyze each step in the multi-staged, complex path of LTBI screening and treatment. (118) A CEA that uses local empirical cascade of care data will enable a realistic assessment of the present performance and efficiency. At the same time, it can identify cascade gaps that influence cost-effectiveness while a sensitivity analyses can help identify cascade improvements that could make the screening more cost-effective.

A systematic review and meta-analysis of study-level observational data from various screening settings and strategies concluded that there are often major losses at different steps in this LTBI screening and treatment cascade. The meta-analysis concluded that out of all individuals intended for screening, 35% were positive and recommended for treatment but only 18,8% of them completed the treatment. (119) Another systematic review concluded that initiation and completion rates of LTBI treatment varies within and across different risk groups and these rates are frequently suboptimal highlighting the need for adherence enhancing interventions.(120) This study reported that among immigrants the initiation of TPT varied between 23 and 97% among people diagnosed with LTBI while the treatment completion rate when started varied between 7 and 86%.(120)

This wide variation highlights the need for local data about LTBI management in order to evaluate any national or local policy in term of effectiveness and cost effectiveness as these parameters should be included in the economic modeling. Another parameter that has a major effect on the cost effectiveness results is the measured outcome with the health-related quality of life (HRQoL) being commonly used and it will be elaborated on in the next chapter.

1.6 HEALTH-RELATED QUALITY OF LIFE

1.6.1 Basic concepts

Cost effectiveness studies of preventive TB interventions can use averted TB cases as an outcome. However, a widely used alternative is quality-adjusted life years (QALY) based on measurements of HRQoL. But what is HRQoL? And how to obtain QALYs?

Developments in health care and medical technologies has resulted in treatments extending life sometimes at the expense of quality of life (QoL) or improved QoL without extending life. Therefore, mortality rates were are not enough to account for the effect of health interventions as it fails to grasp any QoL improvement and cannot be used to assess some interventions like palliative care programs. A health outcome is needed to accommodate for the effect on QoL as well as the extend of life. Hence, the concept of QoL has become center piece for health economic evaluations. (110,121)

QoL can be defined as ‘‘an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social, and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values’’(122). While this definition seems like an all-inclusive concept including all factors affecting a persons’ life, HRQoL accounts only for the dimensions that can be changed by a disease or treatment and therefore it accounts for the dimensions affected by health. (121)

To understand the impact of healthcare interventions and compare across different areas, a common measure needs to be used, a measure that encapsulate the intervention effect on both the length of life and on the HRQoL; hence the QALY has been developed to be used as an outcome in health economic. (123) HRQoL is defined as values assigned to different health states. These values or utilities can be used to calculate QALY which is a value on a scale (0 to 1) with 1 being equal to full health (no health problems), zero equal to death and values in between 0 and 1 reflect a loss of HRQoL (attributed to a health problem). Health state worse than death can be also reflected by a negative value. (110) Through having this health measurement as a main outcome of a cost-effectiveness analysis, comparison can be done across health interventions in different areas in healthcare, forming a tool for policy making and resource allocation. (110)

1.6.2 HRQoL instruments

HRQoL is measured through validated instruments that can be generic or disease-specific.(110,123,124) Generic instruments can be used among any population regardless of the presence of a health condition or disability while the disease-specific instruments are used among a specific group of patients assessing specific symptoms as well as functional and overall health.(110,125) The most commonly used generic instruments include EuroQoL 5 dimensions (EQ-5D) and the short form health survey with 36 items (SF-36), which includes many questions (dimensions) and respondents choose a response from a set of alternatives for each question.(125)

EQ-5D is a validated HRQoL instrument developed by the EuroQol Group.(126,127) The instrument includes a descriptive system of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) where the respondents choose one option for each dimension.(126) Depending on what answer the respondent chose for each dimension, he/she will obtain a QALY score generated from these 5 chosen answers, based on a specific value set decided for the analysis. The instrument is available with 3 levels (EQ-5D-3L), meaning that for each domain the participant choose one of 3 options to describe the health state (no problems, some problems, extreme problems), or with 5 levels (EQ-5D-5L) in which the 5 levels are available (no problems, slight problems, moderate problems, severe problems, extreme problems). In addition, the instrument includes a visual analogue scale (VAS) where individuals rank their health from 0 to 100 on a scale. (126)

Another widely used instrument is SF-36, a validated instrument of 36 questions divided into 8 subscales accounting for physical, social and mental well-being. These subscales are: general health, physical function, bodily pain, vitality, role-physical, social functioning, role-emotional as well as mental health.(128) For each of the subscales, a score from 0 to 100 is obtained based on the answers of the related questions with zero referring to complete disability and 100 is equivalent to no disability.(128,129) In addition to reporting the scores of each subscale, a common way to present the result of this instrument is to calculate 2 scores: a physical component summary and a mental component summary which can be obtained through mathematical calculations. (129) However, these values are not QALYs and cannot be used in health economics, therefore a variation of SF-36 was developed, SF-6D that can be used to calculate a QALY value ranging from 0 to 1 and adapted in economic models. (129)

1.6.3 HRQoL and TB

TB disease affect the psychological, functional, economic and social wellbeing of individuals and therefore HRQoL is an important adjunct outcome in TB programs and interventions, in addition to standard outcomes such as cases averted, cure and survival.(130) QALY has been used in economic evaluations of TB programs as it suits the societal perspective and it can capture several dimension of the effect of the disease, including disability, psychological distress, stigma, side effects of treatment among other factors.(110,131)

Many factors influence the HRQoL which can be related to patient characteristics, such as demographic characteristics, and clinical presentation, or related to the treatment of TB including health system and health financing factors. (130) These factors are summarized in figure 5.

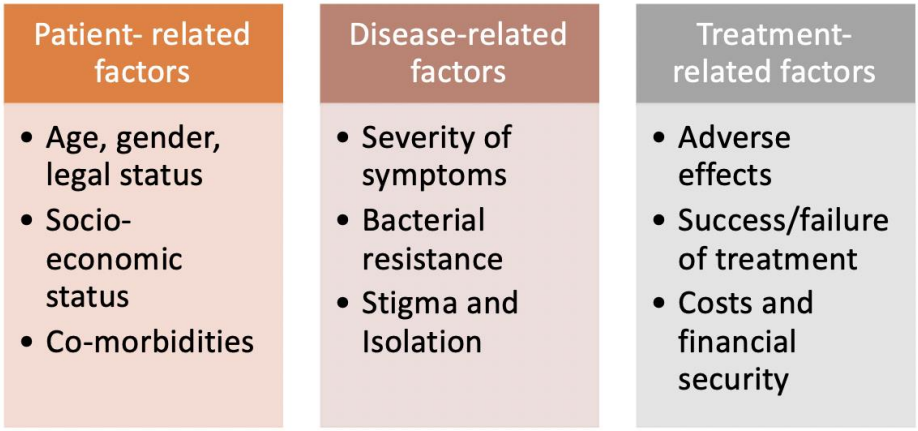


Figure 5 Summary of factors affecting the quality of life of Tuberculosis patients (130)

Due to the complexity of the disease and the interactions between the different factors mentioned above, it can be challenging to quantify impairment of HRQoL due to TB. A recent review showed wide variation in results across countries and patient groups using different instruments. However, the review highlighted that productivity loss, psychological impact and social stigma are common reasons affecting the HRQoL of TB patients. (130) A variety of instruments are usually used to assess HRQoL in the TB field. There is no well-validated TB-specific instruments and most studies have used generic instruments, mainly SF-36 and EQ-5D. (132) However, most studies have been conducted in high-incidence countries and very few studies have been conducted in countries with low incidence where better data is therefore needed due to expected difference in the setting- and patient-related profiles.

Although patients' health status improves with treatment, active TB is associated with a decrease in the HRQOL that might not be restored until months after the end of treatment, or may persist for long periods if there are permanent sequalae from the disease, with physical health possibly recovering quicker than the mental health components.(130,132)

Despite being asymptomatic, a diagnosis of LTBI may cause anxiety and raise concerns among patients in addition to the risk of adverse drug reactions of preventive treatment. (132) This diagnosis may also be miscomprehended as active TB which can increase stigma and psychological stress. (133,134) All these factors can theoretically impair the HRQoL of patients in term of physical, mental and/or social well-being. Nevertheless, there is scarcity of studies assessing this topic in the literature. Canadian and American studies have concluded that there is no significance difference in the HRQoL between LTBI patients and the general population and hence suggested no decrease of HRQoL in economic evaluation.(135,136) However, these studies do not provide deep understanding of the physical, social and mental well-being of this population and do not analyze the factors affecting their HRQoL.

1.7 RATIONALE OF THE THESIS

In Sweden, LTBI screening has been offered for decades to some migrants from high-TB incidence countries, but this screening strategy has never been previously evaluated. More generally, there is an urgent need for research on LTBI screening for persons migrating from high- to low-incidence countries in order to guide future national and international policy and resource allocation. There is little international consensus on which migrants to screen, when and how. WHO and ECDC conditionally recommends such screening but do not elaborate on the conditions or modalities to consider due to a very weak evidence. As a consequence, low-incidence countries, including those where most TB cases are among foreign-born persons, use very different screening approaches and many countries do not perform any migrant LTBI screening at all. There is a need first to describe the LTBI screening and treatment cascade and to identify the obstacles and opportunities to complete the cascade in order to identify areas that need to be improved.

In the Swedish context, participation in health examination is of particular interest as it is the first contact for asylum seekers with the LTBI screening procedures. In addition, there is a need to conduct economic analysis in order both to assess the overall cost effectiveness of the current screening strategy, as well as to determine the most cost-effective targeting of screening. There is a lack of evidence in the literature about cost effectiveness of LTBI screening in general and no CEA has previously been done on LTBI screening in Sweden. Hence the idea of this thesis project. Despite the availability of some CEA studies in low-burden settings, the variation in methods is a challenge that this project also addresses through a review of the methodology and development of a framework for such analyses. Therefore, this project not only generates locally relevant cost-effectiveness data but also helps develop better and more standardized economic evaluation methods for assessing screening of LTBI in migrants.

Finally, there are very few studies reporting the HRQOL of migrants with TB or LTBI and a complete lack of data from the European countries. Therefore, while the HRQoL component of this thesis contributes to the CEA in Sweden, it may also serve as a reference for future TB health economic analyses in Sweden as well as other similar settings.

1.8 PROJECTS RELATED TO THIS PHD

This PhD is part of a larger research project about tuberculosis screening in Stockholm. The work involved two departments at Karolinska institutet - the Department of Global Public Health and Department of Medicine, Solna, The Karolinska University Hospital, the Department of Communicable Disease Prevention and Control, Stockholm Region, and the Public Health Agency of Sweden. The overall aim of the projects was to assess the migrant TB and LTBI screening strategies in the Stockholm Region through a mix of qualitative and quantitative studies in order to both judge the value of the present screening strategy, as well as to identify areas of improvement, with special attention to how to implement screening, referral and treatment to maximize access and adherence. The PhD project of Joanna Nederby Öhd provided data about screening coverage, screening results and completion of the cascade of care data (84), which was used to parameterize the CEA model in the present doctoral project with local empirical epidemiological and implementation data. The author of the present thesis was involved in the design, interpretation of results and writing up the manuscript for the cascade analysis, and was a co-author of that paper, although that paper is not included in the present thesis. Qualitative work and assessment of HRQoL for the present doctoral project was coordinated with Lena Jansson who is studying LTBI screening for pregnant women with migration background in Stockholm (137). The author of the present thesis was involved in the design, data collection, analysis, interpretation of results and writing up the manuscript and was the second author of that paper (128), although that paper is not included in the present thesis.

Beyond the Swedish setting, this doctoral project was linked to a European project (E-DETECT TB) funded by the EU-CHAFEA, which focused on building an international migrant TB screening database through extracting data about TB and LTBI screening and cascade of care in four European countries: Sweden, Netherlands, Italy and UK.(84) As part of E-DETECT TB, economic assessment of LTBI screening in these countries were performed mainly using the model developed within this thesis. Comparison of methods and results between countries is planned for the future, however it is beyond the scope and the timeline of this PhD project.

This project received funding from the Swedish Research Council for Health, Working Life and Welfare (grant 2015-00304), the Swedish Heart and Lung Foundation (grant 2016-0508) and a EU-CHAFEA grant (grant 709624).

2 RESEARCH AIMS

The aim of this doctoral project was to determine the cost-effectiveness of the current strategy of screening for LTBI among asylum seekers/migrants in Stockholm. Ultimately, the project aims to provide policy recommendations to improve and rationalize LTBI screening in Stockholm and Sweden.

The specific research objectives were to:

1) Review and assess the methodology of economic modelling of LTBI screening, understand the major methodological determinants of variability between models and develop a framework for CEA of LTBI screening for asylum seekers in Stockholm.

2) Understand the experiences of asylum seekers attending a health examination in Stockholm, in order to identify gaps and need for improvements.

3) Explore patient experiences with diagnosis and treatment of LTBI as well as their HRQoL and the factors influencing it.

4) Quantify the HRQoL of TB patients in Stockholm.

5) Assess the cost effectiveness of the current LTBI screening strategy among asylum seekers in Stockholm compared to a scenario of no screening.

These objectives are achieved thorough the different studies included in this doctoral thesis and summarized in figure 6 which shows the LTBI screening pathway, the aim of the studies along this pathway and the study design which will be elaborated on in the methods section that follows.

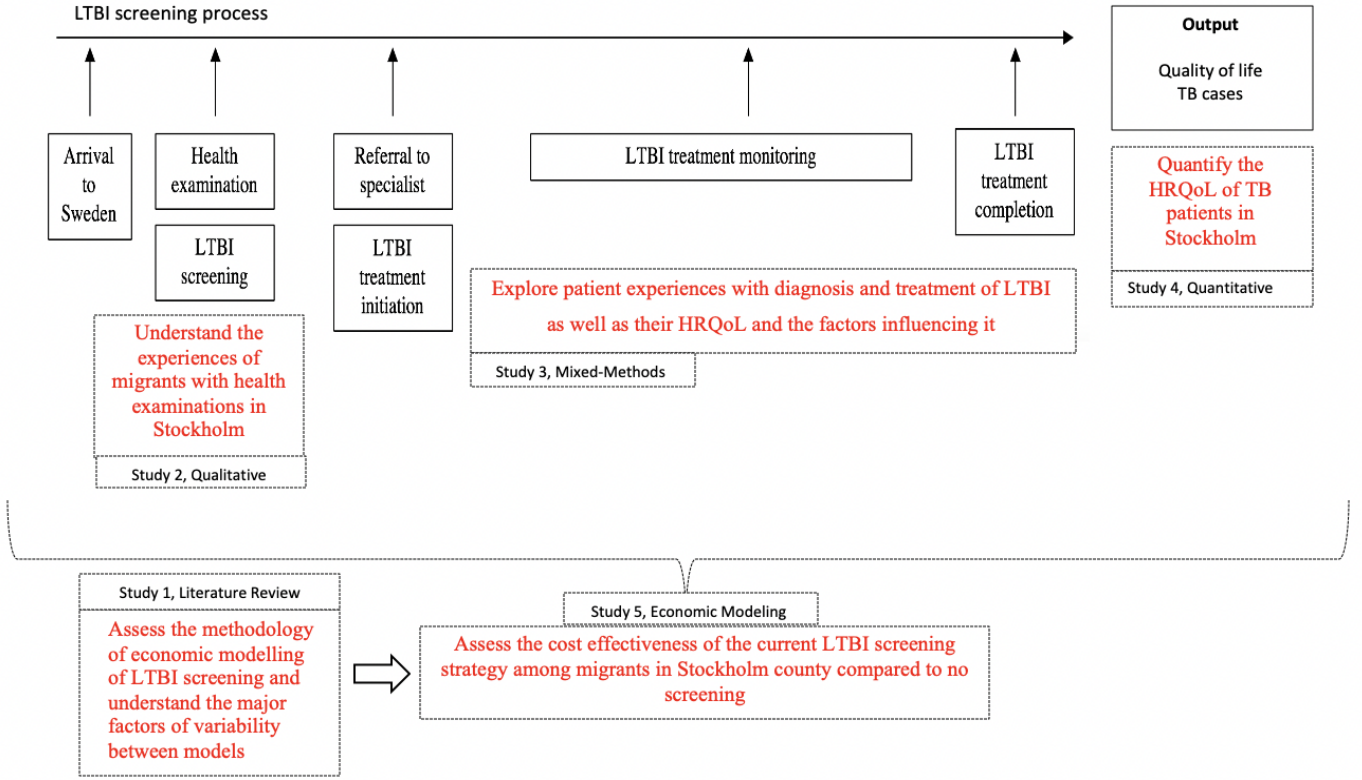


Figure 6. LTBI screening process and the distribution of the thesis objective along its pathway. HRQoL; Health-Related Quality of Life, LTBI; Latent tuberculosis infection, TB; Tuberculosis

3 MATERIALS AND METHODS

3.1 OVERVIEW OF METHODS BY TOPIC

3.1.1 Experiences of Health Examinations (study II)

Study design

Through a qualitative design, researchers can collect and analyze expressive information about values, experiences, motivation and beliefs that orient behaviors that can be difficult to captured with quantitative research techniques.(138) Consequently, this study designed was deemed suitable to explore the experiences of migrants with HE which is the aim of paper 2.

Semi-structured interviews were conducted with migrants based on an interview guide that was developed and piloted before conducting the study. The guide focused on exploring the experiences of the respondents throughout the HE. The guide was revised and ameliorated throughout the process after conducting the first few interviews. The aim of the revision was to include topics of special interest for the respondents that were not initially covered by the interview guide.

Study setting and participants

Participants were recruited among migrants in Stockholm county based on the following inclusion criteria:

1) Legal status: being an asylum seeker or a refugee

2) Age: 16 years or older

3) Fluency in one of the following languages: Arabic, French, Swedish, Somali, Dari or Pashto

Participants were recruited from four different settings around Stockholm county:

1) A language café in the Northern part of Stockholm

2) A Swedish language course in central Stockholm

3) An asylum accommodation in the southern part of Stockholm

4) Through contacts that previously worked with asylum seekers in Stockholm

Data collection

Interviews were conducted between November 2016 and February 2017 by the PhD candidate. A translator assisted during the interviews in Dari and Pashto. Interviews were recorded and lasted between 20 to 25 minutes targeting mainly themes based on the interview guide however probing techniques were used to help the respondents elaborate on their ideas and express their main concerns and observations. Interviews were conducted until data saturation was reached, meaning that no significant new information emerged from participants.

Data analysis

The interviews were transcribed verbatim by the PhD candidate in English language after listening to the recordings several times to ensure complete understanding of the transcripts. The next step was to read the transcript with the senior researcher of the paper and code manually the transcripts and these codes lead to potential categories that were discussed and fitted into a larger theme. Therefore, a thematic analysis was used throughout the process as codes were grouped into categories that matched sub-themes and themes. (139) However, the themes were not created by the authors, rather they were pre-determined based on the availability, accessibility, acceptability and quality (AAAQ) framework. (140) The main categories fitted into one of the four domains of the framework (which are explained in table 2) that was developed under the human rights convention that Sweden ratified and is legally bound to implement. In addition, this framework allows assessment of the health examination in a way that answers the research questions of the study.

Table 2 Definition of the AAAQ framework domains

Domain	Definition
Availability	Functioning public health and health-care facilities, goods and services, as well as programs, have to be available in sufficient quantity within the State party.
Accessibility	Health facilities, goods and services have to be accessible to everyone without discrimination. a- Physical accessibility: health facilities, goods and services must be within safe physical reach for all sections of the population, especially vulnerable or marginalized groups b- Economic accessibility (affordability): health facilities, goods and services must be affordable for all. c- Information accessibility: accessibility includes the right to seek, receive and impart information and ideas concerning health issues.
Acceptability	Health facilities, goods and services must be respectful of medical ethics and culturally appropriate and designed to respect confidentiality and improve the health status of those concerned.
Quality	Health facilities, goods and services must also be scientifically and medically appropriate and of good quality.

Source: UN Economic and Social Council, 2000. General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12 of the Covenant). UN Committee on Economic, Social and Cultural Rights (CESCR) 2000 (140)

3.1.2 Health-related Quality of Life (study III and IV)

Study design

HRQoL data was performed through cross-sectional design for LTBI patients and a longitudinal design for TB patients. Survey instruments were used to collect data from TB and LTBI patients, respectively. Survey research can be defined as “collecting information form a sample of individuals through their responses to questions”.(141) Using surveys that embedded HRQoL measurement tools was considered suitable to analyze HRQoL in light of the different variables of interest. This methodology follows the quantitative approach as outcomes were measured and analyzed quantitatively using statistical methods. However, as one of the objectives was to understand the factors influencing the experiences and HRQoL

of LTBI patients, qualitative interviews were conducted with a subset of these patients and analyzed in an integrated way with the quantitative data, which led to a mixed-method approach for study III (142), while study IV was solely quantitative. Another difference between the two studies is the design, as data from LTBI patients was collected at one point in time while for the TB patients a cohort study design was used with a follow-up assessment of HRQOL after 6 or 12 months depending on the treatment period. (143,144) Finally, the TB cohort was compared to the LTBI cohort which was considered a suitable comparison due to the similarity of socio-economic characteristics. The LTBI cohort was compared to a reference group consisted of the general population of Stockholm. Data about the general population of Stockholm was obtained through a regional survey by the county council "Stockholm hälsa 2014"(145) and was judged as the most up-to-date suitable local data source.

Survey development

A survey was developed and tested which included questions about basic socio-demographic characteristics, previous medical history (including TB history), diagnosis, treatment and side effects in addition to two validated instruments: the EQ-5D-3L instrument to assess HRQoL and the Refugee health screening-15 (RHS-15) instrument to screen for mental health issues among people with a migration background (146). The survey was available in the languages most commonly spoken by TB patients in Stockholm: French, English, Swedish, Arabic, Dari, Tigrinya, Somali, Mongolian. The qualitative interviews conducted for the mixed methods study were facilitated by an interview guide that was developed, tested and then re-adjusted after the first few interviews to include topics of interest that patients touched upon and were missed in the preliminary guide.

Inclusion and exclusion criteria

To be included in the Survey, patients had to fulfill the following inclusion criteria:

1) Age: 16 years old and older

2) Medical diagnosis: TB or LTBI at the Infectious Disease or Paediatric clinics in Karolinska University Hospital, Sweden.

3) Language skills: fluent in French, English Swedish, Arabic, Dari, Tigrinya, Somali or Mongolian.

LTBI Patients with disabling medical conditions (HIV, organ transplant, dialysis, systemic rheumatic disease, ect) that were indications for LTBI screening other than country of origin were excluded.

Data collection

Patients were identified through electronic patient records at the hospital and recruited consecutively between September 2017 and June 2018. Consecutive sampling was considered a suitable equivalent to probability sampling technique for this study and all patients that met the inclusion criteria during the study period were invited to participate in the survey.(147) For the LTBI group data was collected at one time point, either at the

beginning of the treatment, during or at the end. For the TB group, data was collected at 2 point in time; at the beginning of the treatment (first 2 weeks) and at the end (6 or 12 months).

A subset of LTBI patients who participated in the survey were asked to participate in a qualitative interview which took place immediately after the survey was filled based on their socio-demographic characteristics. Thus, a parallel convergent design was used, which allows the examination of qualitative and quantitative data in a concurrent fashion. The advantage of such design is reduced time of research and decreased risk of non-participation, which could be suspected in this patient group if a sequential design was used instead (eg. interviews taking place during a follow up visit). (148,149) Interviews were conducted until data saturation was reached.

Sample size

Sample size calculations were based on a 5 % significance level and 80% power. A 9% difference in the HRQoL of LTBI patients compared to a control group (general population of Stockholm) was deemed suitable from the literature (136) leading to a required sample size of 52 LTBI patients. For the TB cohort, it was assumed that the HRQoL would increase by 15 % by the end of the treatment and therefore 36 TB patients were required to detect this difference.

Data analysis

Data from the surveys were entered manually in Excel. The results of the 5 EQ-5D domains were dichotomized into no problem or problem (merging some and severe problems). In addition, these scores were used to generate the utility scores. Therefore, HRQoL data were presented as following: a) counts (%) of patients with problems in each domain b), mean/median EQ-5D Visual Analogue Scale (VAS), c) mean/median of the utility scores.

There were 3 different ways to compare the EQ-5D scores between 3 different populations:

1) Comparing HRQoL at the start and end of treatment among TB patients

2) Comparing HRQoL between LTBI patients and TB patients at start of treatment

3) Comparing HRQoL between LTBI patients and the general population of Stockholm

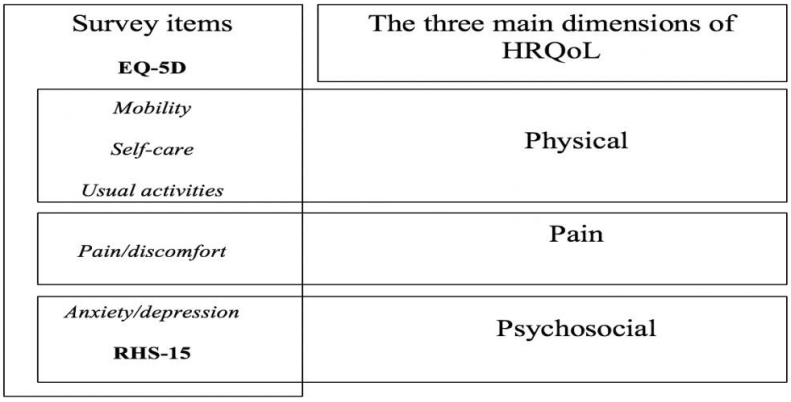
The utility scores were obtained by using a HRQoL value sets. The Swedish experience-based value set for EQ-5D was used in study III, while the UK hypothetical value set was used in study IV concerning TB patients.

For the RHS-15 instrument, data were dichotomized into positive or negative as per guidelines of the instrument (146) and results were presented in term of counts (%) of patients who screened positive for mental health concerns.

Data analysis for the LTBI patients included both qualitative and quantitative data therefore a mixed-method integration framework was used based on the conceptualization of HRQoL dimensions by Cherepenov et al. (150) which determines three main dimensions for HRQoL: physical, psychosocial and pain.

The qualitative interviews were transcribed verbatim in English and read thoroughly by 2 researchers that coded the transcripts manually and then classified the codes under emerging categories that were linked to one of the 3 dimensions of HRQoL by Cherepenov et al. The quantitative data was also classified within this framework with the mobility, self-care and usual activity domains of EQ-5D corresponding to the physical dimension of HRQoL; pain/discomfort corresponds to pain, anxiety/depression along with the RHS-15 score correspond to the psychosocial dimension (illustrated in figure 7). Within each dimension, the qualitative and quantitative data were compared and contrasted and results were shown in a mixed-method meta-inferences indicating if the data reinforce and reassure each other ("confirmation"), contradict and negate each other ("discordance") or if one data set explain and expand the understanding of the other ("expansion")(149,151) .

Figure 8 Matching the survey items to the main dimensions of HRQoL



3.1.3 Cost-effectiveness analysis

Literature review (study I)

A review of the literature was conducted project to assess the methodology of LTBI CEA and develop a framework for the CEA to be used in this project. Three electronic databases (Cochrane Library, Medline and EMBASE) were searched for relevant studies in the filed with no limitation in term of language or time. In addition, reference lists of other systematic reviews were manually searched to make sure not to miss any potential study.

Analysis

Relevance of the studies was assessed based on inclusion and exclusion criteria that are summarized in table 3, these criteria were used by the first 2 authors of the paper in order to review titles/abstracts first and then the full text. Exclusion of studies was decided on and discussed with the senior author of the paper while documenting the reason of exclusion at different stages. The quality assessment of the studies was done using the Drummond checklist for economic evaluation of health programs, 2nd edition (110).

Data from the included studies were extracted into four main data extraction sheets: 1) general economic model characteristics 2) disease and interventions characteristics 3)

program performance 4) target population characteristics. It is to note that meta-analysis of the data extracted was beyond the aim and scope of this review and therefore not performed.

Results from the studies were analyzed and the main input parameters affecting the models' outcomes were summarized in a framework along with the preferred characteristic of the economic models depending on the economic analysis perspective. This framework was largely built based on the Drummond checklist(110), a well-known standard checklist in health economics, while adding some specific aspects for LTBI screening.

Table 3 Inclusion and exclusion criteria for studies in the literature review of LTBI screening

Population	Inclusion criteria	Migrants, immigrants, refugees, asylum seekers, foreign born
	Exclusion criteria	All other populations, specific populations with certain diseases or if the study did not explicitly mention a target population
Intervention / comparators	Inclusion criteria	Assessment of an intervention or a comparison of at least two options with "no screening" as one of the comparators.
	Exclusion criteria	The different options are not compared to "no screening" strategy.
Outcome	Inclusion criteria	ICER, net benefit or difference in cost
	Exclusion criteria	Study does not report an ICER, net benefit or difference in cost
Study design	Inclusion criteria	Full text article that include an economic evaluation (CEA, CUA, CMA, CBA)
	Exclusion criteria	Study does not include an economic evaluation or if it is a review or abstract.

ICER, incremental cost effectiveness ratio; CEA, cost effectiveness analysis; CUA, cost utility analysis; CMA, cost minimization analysis; CBA, cost benefit analysis.

Markov modelling (study IV)

Based on the framework generated through the literature review, a Markov model assessing the CEA of LTBI screening was developed in Excel comparing the current LTBI migrant screening strategy to a hypothetical scenario of no systematic LTBI screening/treatment. A societal perspective with a 50-year time horizon was chosen for the analysis with 2 main outcomes: HRQoL and averted TB cases. Therefore, ICER results were presented in term of marginal cost in Swedish krona (SEK) per QALY gained and marginal SEK per prevented case, respectively. When results are presented in term of SEK per prevented case, the analysis is considered a cost effectiveness analysis (CEA), while presenting the results in term of SEK per QALY falls under the cost utility analysis (CUA) umbrella.(110) Both costs and HRQoL data were discounted by 3% per annum according to the current Swedish recommendations. (117)

The Markov model included 5 mutually exclusive health states as shown in figure 5, each individual move between these states according to his/her predicted health status at each cycle (which was set to 6 months):

1) "Healthy" : a person with no TB and no LTBI diagnosis

2) "LTBI state" : a person with undiagnosed LTBI or diagnosed but untreated or unsuccessfully treated LTBI

3) ”Treated LTBI state” : a person successfully treated LTBI

4) ”TB state” : a person with active TB disease

5) ”Dead state”: death

To simplify the model and avoid having additional health states depending on the sensitivity/resistance of the bacterium, the TB state was averaged to include sensitive TB (87%), mono-resistant TB (10%) and MDR-TB (3%) to reflect the epidemiological situation in this cohort.

Moving between the health states was determined by the time of the cycle (as the reactivation rate is higher in the first 2 years) and epidemiological probabilities which itself depends on the age of the individual. Therefore, it was decided to run the model for 5 different age groups (1-12; 13-18;19-34;35-54; and 55+).

Data used in the economic modelling

The LTBI cascade of care data was based on empirical data from a cohort of all migrants attending HE in Stockholm between January 1st 2015 and December 31st 2018. The cohort consisted of 5470 screened individuals. Data about their screening results, rate of referral to specialists and rate of treatment initiation and completion were extracted from electronic primary (HE and screening results) and specialist (evaluation of LTBI, treatment initiation and treatment completion) medical records linkable through personal identifiers to each other and to a registry of asylum seekers eligible for HE (demographic information, including country of origin), which was based on data from the Swedish Migration Agency. This record-linkage cohort study (84) is in the list of articles related to this thesis co-authored by the PhD candidate.

Aligned with the societal perspective choice, different direct and indirect costs were included in the analysis, which were mainly derived from local databases, regional references and discussions with the Public Health Agency of Sweden. Direct medical costs included costs of the screening as well as treatment when initiated. Direct non-medical costs included cost of translators and transportation while the indirect costs were quantified in term of productivity loss.

A conservative assumption was made to calculate the productivity loss based on the lowest 10th percentile monthly salary in 2016, which was 22 000 SEK, plus 31% social fees paid by employer to the state.(152,153) Therefore, the total monthly productivity loss was 28 912 SEK, divided into 21 workings days with 8 working hours/day which leads to a cost of 172 SEK/hour. This cost has been added to all ages, as for children it was assumed that one adult will miss work to assist the child. The reason behind using the lowest 10th percentile salary is the difficulty for asylum seekers to get into the job market and therefore a conservative assumption would decrease the risk of any overestimation of the cost effectiveness of the screening program, since most of the productivity loss would be related to active TB.

Despite a lack of clear guidelines of cost effectiveness threshold in Sweden, the National board of Health and Welfare usually consider an intervention to be very cost effective when the ICER is below 100 000 SEK/QALY, cost effective when the ICER is below 500 000,

moderately cost effective when the ICER is between 500 000 and 1000 000 SEK/QALY and not cost effective above 1 000 000 SEK/QALY.(41)

3.2 ETHICS

The cost effectiveness analysis part of the thesis did not need any ethical permit as it did not involve collecting information from individuals. For study II,3 and 4, which involved conducting interviews/surveys, an ethical permit was needed. The qualitative study II was granted an ethical approval by the regional Ethical Board in Stockholm county (reference Number: 2016/1648-32). Another permit was approved by the same board to conduct study III and 4 (reference Number: 2017/1595/31). As mentioned in these approvals, the major ethical concerns are related to the integrity of asylum seekers and TB/LTBI patients. Diagnosis can be linked to stigma and fear. Therefore, interviews can raise feelings of discomfort if not conducted in a careful manner. Asylum seekers might fear that their answers will affect their asylum process due to the suspicion that researchers work closely with the migration office, therefore the credibility and neutrality of the researchers is another major ethical challenge that need to be clarified and addressed before conducting any study. Finally, participants might fear that any statement or information they give will be linked in the future, and the anonymity topic should be addressed while conducting this research.

For all studies, informed consent was obtained from respondents after introducing the purpose of the study and taking their approval for participation. The respondents were also informed orally and through the informed consent forms about their right not to answer questions and to terminate the participation without giving an explanation at any time. Finally, the respondents were informed about the confidentiality of the information and that all data will be analyzed anonymously. For study II, asylum seekers were informed verbally and through the written informed consent that the research is done with no connection to the migration office and the information shall not be shared with any authorities rather it is strictly used at Karolinska Institutet for research purposes.

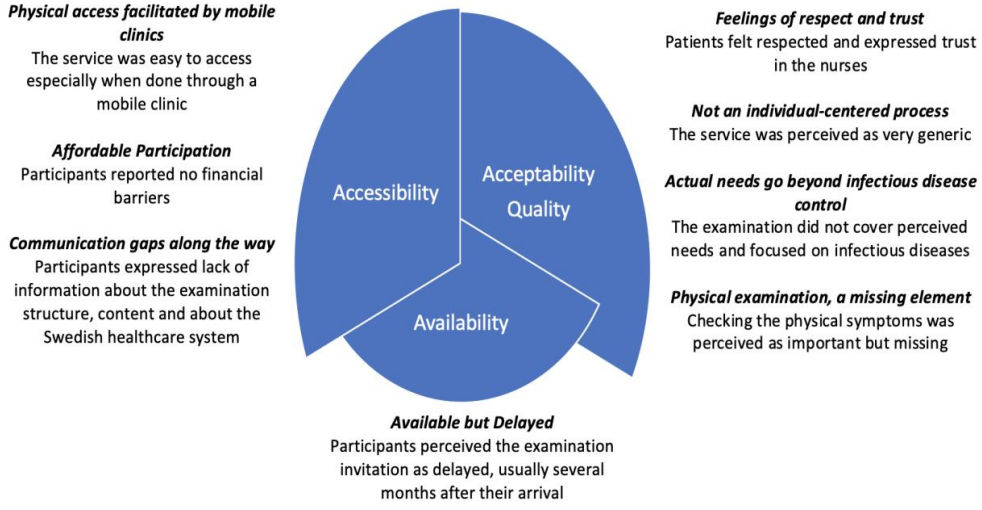
4 RESULTS

4.1 EXPERIENCES OF HEALTH EXAMINATION (STUDY II)

Eighteen participants were interviewed to share their experiences of health examinations in Stockholm. Most of the participants (13) were men and the age range varied between 18 and 48. Sixteen underwent the health examination while the other two had been invited but not participated at the time of the interview. The results of the study are summarized under the four areas of the AAAQ framework presented in figure 8. Overall, there was a perceived good availability, affordability and physical accessibility, especially facilitated by mobile clinics. Acceptability was high among the interviewees who felt respected and trusted the healthcare system.

Concerns were raised about the delay in performing the examination which has implications on controlling infectious diseases as expressed by the interviewees. They also expressed the need for more information about the purpose and structure of the examination, as well as information about the Swedish healthcare system and their rights as refugees and asylum seekers to seek healthcare. Concerns were raised about the health examination in terms of its scope as interviewees did not experience the service as individual-centered, rather as a very generic evaluation for everyone regardless of their actual needs or health status. In addition, the examination was perceived to focus mostly on infectious disease control and not covering enough other important aspects for the interviewees, such as mental health and dental care. Interviewees questioned the value of the examination and screening for diseases while not offering effective treatment for all of them, mainly due to legal status and the restrictive rights asylum seekers are entitled for.

Figure 9 Main results of qualitative study about health examination in Stockholm



4.2 HRQOL RESULTS (STUDY III AND IV)

As shown in table 4, patients reported problems on two domains mainly: pain/discomfort and anxiety/depression. The highest percentages of reported problems were observed among TB patients at the beginning of the treatment followed by TB patients at the end of the treatment. In addition, 38% of LTBI patients scored positive on RHS-15.

Table 4 EQ-5D results for each domain, utility score and VAS score for LTBI and TB patients

	TB group				
	Start of treatment *n* (%)	End of treatment *n* (%)	*P* value*	LTBI group	*P* value†
Patients with some or severe problems in each EQ-5D dimension					
Mobility	6 (15)	9 (26)	0.182	8 (7)	0.161
Self care	3 (8)	0	—	2 (2)	0.091
Usual activities	8 (20)	5 (14)	0.683	8 (7)	0.030
Pain/discomfort	22 (55)	14 (40)	0.267	26 (24)	<0.001
Anxiety/depression	16 (40)	12 (34)	0.773	30 (28)	0.153
Utility scores					
Mean (95%CI)	0.72 (0.62–0.832)	0.84 (0.79–0.9)	0.021	0.84 (0.79–0.88)	
Median [IQR]	0.79 [0.68–1]	0.84 [0.72–1]		1 [0.79–1]	<0.001
VAS scores					
Mean (95%CI)	72 (65–78)	82 (77–87)	<0.001	80 (76–83)	
Median [IQR]	82 [77–87]	87 [70–95]		90 [75–100]	<0.001

* Comparing start of treatment to end of treatment for active TB patients. McNemar's test used for percentage reporting problems on EQ-5D domains; paired *t*-test for EQ-5D utility and VAS scores.
† Comparing LTBI to active TB at start of treatment; χ^2 test used for percentage reporting problems on EQ-5D domains; Wilcoxon rank sum test for EQ-5D utility and VAS scores, due to skewed data.
EQ-5D = Euroqol-5 dimensions; VAS = visual analog scale; LTBI = latent tuberculosis infection; TB = tuberculosis CI = confidence interval; IQR = interquartile range.

The HRQoL of TB patients at the beginning of treatment phase was quantified as 0,72. This value increased to 0,84 by the end of the treatment, an increase that was statistically significant. The HRQoL of LTBI patients was reported as 0,84 which was similar to the HRQoL of the general Stockholm population. The same trend of changes was observed when analyzing the VAS score means and medians. The results show an increase of the VAS score through completion of TB treatment.

Among the 47% of TB patients who experienced ADRs, the most common ones were nausea, rash and body pain, reported by 25%, 15% and 10%, respectively. 41% of LTBI patients reported ADRs; Nausea was reported by 18% while 11% reported dizziness. In addition, LTBI patients experienced fear and worry created through the LTBI diagnosis, which could be misunderstood as active TB and therefore concerns were raised about the fatality of the disease, its contagiousness and future uncertainties. This can explain the findings that anxiety depression was reported as a problem in the EQ-5D domain by 27.8% of LTBI patients while 38% screened positive for some mental health concerns using RHS-15. Other factors that were identified through the quantitative research and can explain the deterioration of the mental health among patients include: unclarity about LTBI diagnosis, future uncertainties and the fear of infecting other family members. Table 5 summarizes the mixed-methods results of study III.

Table 5 Joint display of quantitative, qualitative and mixed methods inference results

Health dimensions	Quantitative findings % scoring problems (95% CI)	Qualitative findings Subcategories and quotes	Mixed method meta-inference
Physical	Mobility : 7.4 % (2.4;12.4)	***Daily routines maintained***	**Confirmation** patients ability for physical movement and functional activities was not compromised by the disease or the treatment
		The medication doesn't interfere with anything in my daily life. (F, 37)	
	Self-care 1.9% (1;4)	*I go to school as usual, there are no changes, life is the same as before. (M, 38)*	
		Manageable physical side effects	
	Usual activities: 7.4 % (2.4;12.4)	*I was very happy to start the treatment… it is very easy and I do not experience any side effects. (F, 27)*	
		It goes ok with the treatment, I was a little tired in the beginning with some taste change in the mouth but I have to accept and solve the small side effects… I outweighed the benefit and the side effects. (F, 23)	
Pain	Pain/Discomfort: 24.1 % (15.8;32.2)	***Experienced pain***	**Expansion** pain and discomfort reported might be attributed to Gastrointestinal side effects of the medication
		I feel pain in my stomach after I started the treatment. I had stomach pain before but with the tablets it came back. (M, 32)	
		my wife and I have problems with stomach pain as we take it in the morning we feel some pain that decreases during the day. (M, 31)	
Psychosocial		***Ambiguous threat***	**Expansion** Patients' mental health was compromised due to unclarity about the disease itself, the future and the fear of infecting others
		I googled a lot about tuberculosis, I was afraid that I might die because of it or to find out that it is a dangerous disease. . (F, 25)	
	Anxiety/Depression : 27.8% (19.9;36.3)	*I was thinking so much and I was scared when I found out about TB , it is not good and who infected me? I just think a lot when I try to sleep I cannot sleep (F ,40)*	
		Fear of being contagious	
	positive RHS-15 : 38% (28;47)	*I have a baby that I was breastfeeding but after I got diagnosed I stopped breastfeeding him as I should not… I do not want to transmit the disease to him. (F,34)*	
		The midwife gave me information about what I should get but I searched myself a lot of information. I felt a little worried that I might infect my children even though I see that I did not infect them but still I am worried anyway. (F,23)	
		I was scared and I said to myself I cannot even take the metro because I might infect others. (M,55)	
		Future uncertainties	
		Even now and after finishing the treatment we will still be worried about this disease, will we heal or will it activate to another disease, I don't know. (M, 31)	
		I think about the future, when I get older what if tuberculosis comes back and gets active then… (F,40)	

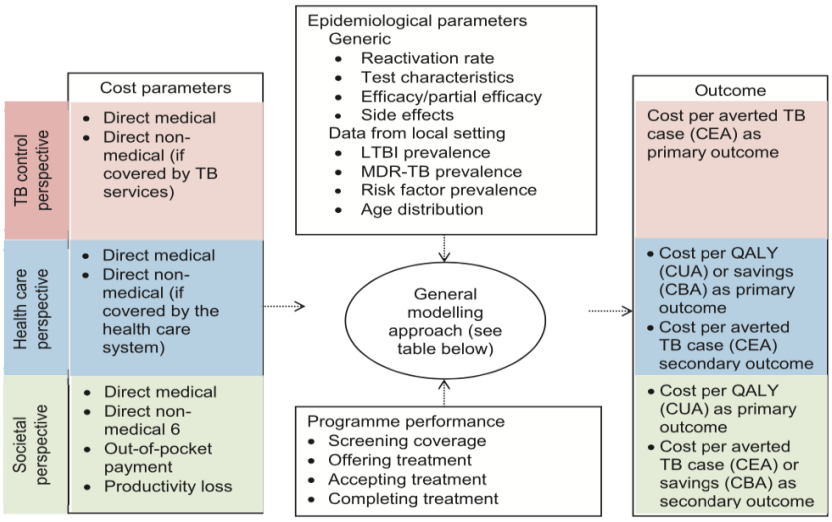
4.3 ECONOMIC ANALYSIS (STUDY I AND V)

The literature review included 10 studies from 4 different low-incidence countries (Canada, USA, UK and Norway). The economic modelling was performed through a transmission model in one study while the rest used a Markov model (with or without a decision tree) to estimate the future costs and effects of LTBI screening. The screening process varied among settings in terms of target groups, procedures, screening tests and treatment eligibility, which made it hard to compare between the studies. Another major difference detected was the type of costs included which was determined by the economic perspective of the study. Five studies adopted a healthcare perspective including all costs paid by the healthcare system, while three studies included costs paid by governmental agencies (governmental perspective), one study included both governmental costs as well as out of pocket payments. Finally, one study adopted a societal perspective and included all types of costs incurred, including productivity loss.

The review showed a wide variation in terms of epidemiological, test accuracy, efficacy and ADR assumptions. Assumed TPT efficacy ranged between 65% till 100%. The program performance parameters in term of screening coverage, treatment initiation and completion rates also varied, and these parameters were main drivers of variation in cost-effectiveness results, as demonstrated by sensitivity analyses. Only 2 studies reported the proportion of treatment being offered when the person is eligible, however studies usually specified the treatment initiation and completion rates with the majority of studies using empirical data while 3 studies used assumptions. Finally, reactivation rates and LTBI diagnostic tests characteristics were also important determinants of cost-effectiveness as shown in the sensitivity analysis, however these parameters where quantified differently across studies. In some studies, the reactivation rates were stratified according to time since infection, HIV status or the assessment of reactivation risk.

Based on the literature review findings a framework to help standardizing approaches and methodology used for economic modeling of LTBI screening among immigrant in low incidence settings was developed. This framework was influenced by the Drummond checklist (110) while tailoring it to fit LTBI screening in immigrants. This framework (figure 8) was used to develop the Markov model assessing LTBI screening in different cohorts compared to no screening in place in Stockholm in study V.

Figure 10 Framework for economic modelling of LTBI screening in migrants to low TB incidence countries.



General modelling approach

- Use a Markov model with a long time horizon to capture the effect of the disease over time.
- Discount future costs and effects according to the national discount rate.
- Specify the perspective and the administrative level of the analysis (state if provincial/state/regional level perspective).
- Use of the societal economic perspective if possible.
- Adapt the costs to the level and perspective and justify the exclusion of any relevant costs.
- Clarify if direct medical and non-medical costs are covered by patients, healthcare or a third party, and include it appropriately based on the perspective chosen.
- Add out-of-pocket costs to the analysis, otherwise justify its exclusion.
- Use the most recent values derived from systematic reviews to quantify epidemiological parameters if national specific data do not exist.
- Use local costing data if possible. If using costing data from another setting, adjust and inflate appropriately.
- Include programme performance parameters and cover as much as possible of the LTBI cascade with data from the specific setting, otherwise use data from literature reviews or other studies with a similar context.
- Include partial efficacy in the case of incomplete LTBI treatment.
- Include MDR-TB data in settings where drug resistance is a known phenomenon.
- Perform sensitivity analysis, particularly for parameters that are not based on solid evidence but also for relevant scenarios of programme performance.
- Interpret the results carefully within the context studies and qualify clearly any generalisation.

TB=tuberculosis; LTBI= latent tuberculosis infection; MDR-TB= multidrug resistant TB; CEA= cost effectiveness analysis; QALY= Quality adjusted life years; CUA= cost utility analysis; CBA= cost benefit analysis.

The economic model predicted that the present screening approach conducted during four years (2015-2018) would prevent 25 cases in the study cohort over a 50-year time horizon compared to no screening. The majority of cases (64%) would be prevented among adolescents (age 13-19). Table 6 presents the results of CEA and CUA by age group and country TB incidence categories. The CUA showed that the ICER is lowest among the age

group 13-19 at to 303 881 SEK/QALY. This was the only ICER below the 500 000 SEK/QALY threshold. The ICERs of screening the age groups 0-12 and 20-34 were between 500 000 and 1 000 000 SEK/QALY while screening older groups generated ICERs > 1 000 000 SEK/QALY. The same trend was observed with the CEA.

Within each age category, the ICER generally got lower as the country TB incidence got higher. For example, in the age group 20-34 the ICER was around 500 000 SEK/QALY for immigrants from highest-incidence countries (> 300/ 100 000), and gradually increased to 1 431 023 SEK/QALY in immigrants from the lowest-incidence countries (<50/100 000) (table 6).

As predicted through the literature review, the cascade of care parameters largely influenced the economic analysis results. Our analysis of the screening cascade (84) found that the rate of referral to TB clinic following a positive IGRA was around 70% for groups younger than 20 years old which drops drastically to less than 30% for the older groups. This affected the rates of initiating treatment among IGRA positive patients with the highest rates among younger patients (55% for age group 0-12, 66% age group 13-19) while it dropped to 17 % in the age group 20-34 and to around 4% for older cohorts. Rates of finishing initiated treatment were high among all groups.

In a scenario analysis for the age group 20-34, empirical cascade parameters (31% visiting TB clinic, 17% of those starting treatment and 83% of them completing treatment), were changed to match the empirically observed data for the age group 13-19 (70% visiting TB clinic, 65% of those starting treatment and 94% of them completing treatment), the ICERs decrease to 274 626 SEK/QALY, and 208 812 SEK/ prevented case, hence increasing the cost effectiveness of the screening approach in that age group.

Table 6 Results of Cost effectiveness analysis by age groups and country and by TB incidence in country of origin

Age groups (years) disaggregated by incidence in country of origin (per 100 000)	Number of people screened	Total cost, no screening programme (SEK)	Total cost, present screening programme. (SEK)	Total incremental cost (SEK)	Total QALY, no screening programme	Total QALY, present screening programme	Total incremental QALY	ICER (SEK/QALY)	Active TB cases, no screening programme	Active TB cases, present screening programme	Incremental cases prevented	ICER (SEK/prevented case)
0-12	**370**	**306 730**	**755 540**	**448 810**	**9554,029**	**9554,584**	**0,555**	***808 667***	**2,22**	**1,4097**	**0,8103**	***553 881***
<50*	66	60 869	142 753	81 884	1704,19	1704,31	0,12	***682 367***	0,44	0,28	0,16	***511 775***
50-100*	56	38 811	104 434	65 623	1446,06	1446,13	0,07	***937 471***	0,27	0,18	0,09	***729 144***
100-199	116	67 102	199 042	131 940	2995,49	2995,6	0,11	***1 199 455***	0,44	0,3	0,14	***942 429***
200-299	40	68 977	128 241	59 264	1032,65	1032,8	0,15	***395 093***	0,53	0,32	0,21	***282 210***
>= 300	92	105 933	226 407	120 474	2375,41	2375,63	0,22	***547 609***	0,78	0,49	0,29	***415 428***
13-19	**1752**	**4 292 400**	**7 859 472**	**3 567 072**	**44888,5176**	**44900,256**	**11,7384**	***303 881***	**33,288**	**17,30976**	**15,97824**	***223 246***
<50*	75	94 390	211 914	117 524	1922,14	1922,38	0,24	***489 683***	0,7	0,38	0,32	***367 263***
50-100*	106	446 932	736 454	289 522	2714,71	2716	1,29	***224 436***	3,53	1,8	1,73	***167 354***
100-199	1355	3 246 784	5 976 854	2 730 070	34717,28	34726,25	8,97	***304 356***	25,11	13,1	12,01	***227 316***
200-299	164	766 108	1 243 424	477 316	4199,66	4201,89	2,23	***214 043***	6,07	3,08	2,99	***159 637***
>= 300	52	112 769	212 881	100 112	1332,4	1332,7	0,3	***333 707***	0,87	0,46	0,41	***244 176***
20-34	**2007**	**6 275 889**	**9 479 061**	**3 203 172**	**50597,072**	**50601,487**	**4,4154**	***725 455***	**48,168**	**42,42798**	**5,74002**	***558 042***
<50*	273	401 139	773 205	372 066	6885,14	6885,4	0,26	***1 431 023***	2,97	2,62	0,35	***1 063 046***

50-100*	355	760 624	1 278 004	517 380	8951,77	8952,29	0,52	***994 962***	5,77	5,07	0,7	***739 114***
100-199	727	1 965 536	3 082 341	1 116 805	18329,76	18331,15	1,39	***803 457***	15,09	13,22	1,87	***597 222***
200-299	314	1 025 100	1 532 197	507 097	7915,78	7916,52	0,74	***685 266***	7,93	6,94	0,99	***512 219***
>= 300	338	1 406 853	1 995 310	588 457	8518,99	8520,01	1,02	***576 919***	10,96	9,58	1,38	***426 418***
35-54	**1125**	**4 520 250**	**6 273 000**	**1 752 750**	**26 059**	**26 060**	**0,79**	**2 225 714**	**32,625**	**31,5**	**1,125**	**1 558 000**
<50*	139	348 520	549 066	200 546	3220,94	3221	0,06	***3 342 433***	2,51	2,43	0,08	***2 506 825***
50-100*	248	954 802	1 338 145	383 343	5744,88	5745,05	0,17	***2 254 959***	6,99	6,76	0,23	***1 666 709***
100-199	288	1 079 057	1 521 948	442 891	6671,64	6671,83	0,19	***2 331 005***	7,89	7,64	0,25	***1 771 564***
200-299	182	851 081	1 143 936	292 855	4215,17	4215,32	0,15	***1 952 367***	6,26	6,05	0,21	***1 394 548***
>= 300	268	1 280 919	1 714 279	433 360	6206,81	6207,03	0,22	***1 969 818***	9,42	9,12	0,3	***1 444 533***
55+	**219**	**768 909**	**1 127 412**	**358 503**	**3 577**	**3 578**	**0,09**	**4 092 500**	**4,60**	**4,51**	**0,09**	**4 092 500**
<50*	27	79 213	121 963	42 750	441,12	441,13	0,01	***4 275 000***	0,48	0,47	0,01	***4 275 000***
50-100*	26	93 347	136 117	42 770	424,72	424,73	0,01	***4 277 000***	0,56	0,55	0,01	***4 277 000***
100-199	99	326 552	486 694	160 142	1617,31	1617,34	0,03	***5 338 067***	1,97	1,92	0,05	***3 202 840***
200-299	41	156 172	224 461	68 289	669,71	669,73	0,02	***3 414 450***	0,94	0,92	0,02	***3 414 450***
>= 300	26	100 932	144 416	43 484	424,69	424,7	0,01	***4 348 400***	0,61	0,60	0,01	***4 348 400***

5 DISCUSSION

5.1 GENERAL DISCUSSION

Health examination, an entry point for TB control and health needs assessment

Health examination is the main entry point in Sweden for systematic TB and LTBI screening of asylum seekers and refugees. Therefore, understanding the opportunities and obstacles around this examination is one of the first key steps for optimal and cost-effective screening in this vulnerable group. The results of this thesis are consistent with the available literature about the experiences of asylum seekers and refugees with health examinations in Sweden. Study II along with other research suggest that asylum seekers and refugees in general have a positive attitude towards the health examination and perceive it as an opportunity to improve their health status and learn about the health system. However, several challenges have been repetitively identified in different studies, mainly including: unclarity and communication issues, focus on infectious disease control only rather than all aspects of health, and lack of a person-centered approach. (92,94,95,154)

Unclarity due to miscommunication or lack of information is a main challenge that can compromise the value of the health examination. A survey showed that 36% of participants perceived the communication during the health examination as poor while 55 % report that they received little information about Swedish healthcare through the examination. (95)This unclarity, communication challenges and limited accessibility to information can trigger feelings of insecurity and compromise the perceived value of the examination. (91,92,94,154) Aligned with the findings of this thesis, the communication in HE has been reported also elsewhere to be perceived as a one-way phenomenon rather than an actual dialogue with a healthcare professional. In other words, some participants perceived the goal of the service as the health care provider gathering information from them rather than giving them the information they need, which is an aspect of the HE that should be improved in the future.(94)

Information need to be given clearly to the participants about the purpose of HE, about which diseases they may get tested for, as well as about their rights and the free-of-charge treatment they may receive for certain infectious diseases.

The request for more holistic and comprehensive HE should not be interpreted as critique by participants that too much infectious disease screening is done. On the contrary, they seem to take for granted that this should be included. The concern about the delay of the examination should be tackled as it could have implications for both infectious disease control and the perceived value and willingness to participate in HE. It could lead to fear of disease transmission, both from the participant him or herself to others, as well as from others to the participant, which could indirectly contribute to worry and stress. However, it is worth mentioning that the long delays were mainly observed after the big influx of refugees in 2015-2016. As these numbers substantially decreased the following years, the delays were shortened.

One study showed that 2 out of 3 individuals perceived the HE as a pure communicable disease measure rather than an assessment of the actual health needs, with 55 % of the respondents perceiving that their actual needs were over-looked especially the mental illness aspect.(92)In another study conducted in four different Swedish regions, unmet expectations and health needs were highlighted by interviewees especially in term of mental health needs. (154) As a result, participants can have a feeling of disappointment as the service does not fulfil the image of an adequate examination from their perspective, if not person-centered, covering health in a holistic manner and providing immediate help except for urgent care. (94) In addition, screening and overlooking some health needs, like asking about mental health without offering any support or possible referral, raises an ethical dilemma and might have a negative impact in practice. In the "The ethics of screening: Is 'screeningitis' an incurable disease?" authors discussed the ethical, practical and economic dilemmas of offering screening and treatment to a certain population. The article emphasizes the need to offer treatment following any screening otherwise withholding any intervention can cause more harm than not performing the screening. (155)

A main argument against granting universal health coverage for this vulnerable group is the expected high costs. However, this is not backed up by any evidence in the literature. On the opposite, studies in different European settings showed that more inclusive healthcare packages for asylum seekers can decrease the direct and indirect costs on the long run, and healthcare savings could be achieved through preventing progression to serious and chronic diseases. In addition, these migrants will contribute to the economies of the host country therefore reducing productivity loss is a strong argument for less restrictive healthcare policies. (156–159)

The use of mobile clinic for HE was seen as a favorable approach in this thesis, as well as in other studies (160,161). It may be an effective way to remove geographic and social barriers and therefore potentially increase participation and decrease any delay, especially in case of an influx of high number of asylum seekers in a short period of time.

In summary, we found that the interviewed asylum seekers and refugees overall had a positive attitude towards HE, including TB and LTBI screening, but also saw room for improvements.

Mental and physical components of HRQoL in persons with TB or LTBI

Mental health

Mental health among asylum seekers was not a main focus of this thesis but nevertheless mental health concerns have been a recurrent theme, whether linked to asylum seekers' general health and related HE expectations or an element of HRQoL linked to LTBI screening and treatment or TB disease.

As discussed above, asylum seekers perceived mental health as one of their main needs that should not be overlooked by healthcare and the HE. These qualitative findings are supported by the high prevalence of mental health concerns among asylum seekers and refugees in Sweden, for example in term of high prevalence of depression, anxiety and PTSD shown by

several studies (162,163). Those findings are in line with the high RHS-15 scores found in study III, as well as the high proportion of patients scoring problems on the EQ-5D mental health domain. Many factors contribute to the exacerbation of mental health concerns. Some factors are related to the pre-migration phase such as trauma and exposure to danger and war. However, many factors are related to the post-migration phase in the host country, including uncertainties and worries related to legal questions, unclarity about health care and other welfare systems in the host country and perceived inability to seek and receive the healthcare they need, as shown in this thesis as well as in the literature. (164,165)

Concerns about mental health are common in this vulnerable group regardless of the TB status. However, being diagnosed with LTBI or TB can add another layer of complexity. Fear of reactivation of LTBI can be linked to future uncertainties and compromised mental health as shown in this thesis. The knowledge of a serious and deadly disease being dormant in their bodies can trigger the sense of fear among patients. (132)In addition, TB can be a stigmatizing disease, perhaps more so in their country of origin. Therefore, patients may fear discussing LTBI diagnosis with their family or friends. Stigma is related to the perceived risk of transmission to other members, as well as its association with HIV, low social class and poverty, even in low-incidence countries, which can impact mental health, treatment adherence and clinical outcomes. (166,167)

This stigma is rooted with many misconceptions about TB and LTBI. A study conducted among immigrants in the north of Sweden showed a poor knowledge about TB disease and LTBI. Participants had a negative attitude toward TB along with many misconceptions. Poor health literacy can be linked to inaccessibility of information, a challenge that can be tackled through including more attention to TB education as part of screening programs in Sweden, at least within the high-risk groups to address misconception and increase awareness about prevention. (168) Another important pathway could be through programmatic tackling of mental health as part of TB and LTBI management. Integrating mental health with TB control might be of a good value in a setting such as Sweden where the majority of the LTBI and TB cases are among immigrants who might have limited knowledge about navigating and using healthcare services. (169)

Physical health

Patients on anti-TB medicines, for TB or LTBI, can experience ADR such as skin reactions, gastrointestinal side effects and hepatotoxicity, which is a severe side effect that can lead to treatment discontinuation. Therefore, it is recommended to monitor liver enzymes in patients on anti-TB drugs, especially for persons 35 years of age and older according to the WHO recommendations. (24,49,50) None of the LTBI or TB patients enrolled in study III and 4 experienced hepatotoxicity. However, the sample was small. Patients instead reported milder side effects such as nausea and pain, which can explain the high percentage of reported problems on the pain/discomfort dimension of EQ-5D in both the TB and LTBI groups, although mainly in the TB group.

In term of the physical health dimensions of EQ-5D, very few LTBI patients scored problem on mobility, self-care and usual activities, while a higher percentage of TB patients scored problems on mobility and usual activities dimensions even at the end of the treatment, which

is in line with the fact that TB disease can be severe, lead to a variety of symptoms, disability and discomfort, as well requiring a treatment regimen with several medicines, each which can give several types of ADR.

HRQoL scores

To our knowledge study III and 4 are among the first studies that have quantified the HRQoL of TB and LTBI patients and generated utility scores in a European setting where the majority of patients belong to migrants' population. A similar study, which did not focus on migrants only, has been conducted in the UK using EQ-5D and SF-36 and it showed similar results in term of the high percentage of TB patients scoring problems on pain/discomfort and anxiety/depression dimensions of EQ-5D at diagnosis as well as at 2-months follow up. (170) However, that study did not generate any utility scores. Our results are also in line with the evidence from HRQoL studies conducted in the USA and Canada which showed a significantly lower HRQoL among TB patients compared to LTBI patients and the general population in these settings both during and after treatment. (136,171)However, this thesis as well as the available literature emphasize that in a group of predominantly newly arrived migrants, mental health concerns may also be unrelated to TB and reflect the general QoL issues of migrants like the legal concerns.

The mental health concerns discussed above were not reflected in the utility scores values derived from the LTBI group, as the scores were relatively high and similar to the general population of Stockholm. This can be due to the heavy preponderance of physical items in EQ-5D and its questionable sensitivity to mental health concerns which has been debated in the literature. Some criticize the large focus of EQ-5D on the physical dimension of health compared to the psychosocial aspects. (172,173)In addition, EQ-5D-3L has been criticized for its ceiling effect, a phenomena that occurs when most of respondents declare no problems in a certain dimension, especially compared to SF-12, which was also able to better detect changes in symptom severity.(174,175)In addition, EQ-5D-5L has shown less ceiling effect and better properties a better discriminative power, hence better at detecting changes in scoring within each dimensions, compared to E1-5D-3L, making it more favorable. (176–180)

A head-to-head comparison of the 3- and 5-level version of EQ-5D shows differences between the two instruments. The highest weight for the EQ-5D-5L was for anxiety/depression while it was mobility for the 3L version, emphasizing again the physical health focus of the EQ-5D-3L instrument. (176) The increased sensitivity of the 5 levels version also favors QALY gains even if the changes in utility are smaller, and therefore the 3L and 5L lead to different utility scores which impact cost-utility outcomes in different ways. (181,182) With the current evidence leaning toward the use of the EQ-5D-5L, further research might be needed in the future about the use of EQ-5D-5L among TB and LTBI patients. For this thesis the EQ-5D-3L version was favored due to the availability of the instrument in the languages of the asylum seekers in Stockholm, but when there is no language barrier EQ-5D-5L might lead to better understanding of the HRQoL.

As expected, the mean utility score of TB patients was significantly lower compared to the LTBI group, although it improved by the end of the treatment. This is in line with the findings of the few HRQoL of TB patients in low-incidence countries. None of these studies generated utility scores through EQ-5D and therefore straight forward comparisons cannot be made. However, one study in Thailand used EQ-5D and showed a median EQ-5D score of 0,69 which increased to 0,88 after successfully completing the treatment, similar to our results. (183)

Finally, an LTBI diagnosis might trigger feelings of fear, insecurity and anxiety as discussed before, hence screening without the possibility of providing preventive treatment can cause more harm than not screening and it can be seen as morally wrong. In addition, this thesis showed that screening in many age groups was very costly for healthcare and society, especially in the older groups that have very restrictive access to preventive treatment. Therefore, effectiveness and cost-effectiveness of the LTBI screening program assessed through this thesis is questionable, which will be discussed in the next section.

Cost effectiveness of LTBI screening

Based on the cost effectiveness thresholds used in this thesis, our results suggest that LTBI screening in Stockholm is cost effective only for some age groups, moderately cost effective for others while it is very costly and not cost effective for others. Apart from age, the results were influenced by TB incidence in the country of origin, as well as by factors related to screening and treatment policy. Patient adherence played a minor role in determining cost-effectiveness.

The findings of this thesis showed that LTBI screening was cost effective in the age group 13-19 and therefore it should be continued to be recommended for them, from a resource allocation perspective. Within this age group, the cascade of care indicators show a high referral rate to TB clinics and high treatment initiation and completion rate with low dropouts. Despite the high adherence to treatment in the youngest group (age 0-12), the ICER was higher and the strategy was not as cost effective as for the age group 13-19 years and this was mainly due to the fact that only a small percentage of children are infected and thus diagnosed with LTBI.(84) However, on the individual level LTBI treatment in young children is often even more valuable than for older individuals due to high risk of activation and severe consequences of TB disease. Despite being only moderately cost-effective, screening children aged 0-12 can still be a priority.

For the age group 20 to 34, the ICER falls between 500 000 and 1 000 000 SEK/QALY and deemed as moderately cost effective. Although increasing prevalence of LTBI with age means increasing cost-effectiveness with age, this is counteracted by the fact that a low percentage of these patients are actually offered preventive treatment in Stockholm. Hence, there were screening costs without any clear corresponding utility for the vast majority of persons over the age of 20 years.

The conservative strategy of referring and treating IGRA+ patients has been questioned, especially when comparing to other regions of Sweden where treatment is often generally

offered for patients up to the age of 30 or 35 years, in line with the recommendations of the public health agency. (81,84) Our scenario analysis within the age group 20-34, using higher referral rate of IGRA positive patients and higher treatment initiation/completion rates that matched the rates observed for the 13-19 years cohort, showed an improved cost-effectiveness that fell well below 500 000 SEK/QALY. Therefore, recommending screening for this age group makes sense if treatment is offered to all who are screened positive. The same conclusion was drawn from a study in Norway, a similar setting to Sweden. The cost-effectiveness analysis of their LTBI screening emphasized the importance of increasing treatment initiation among patients up to the age of 35 years to make it cost effective. (184)

For individuals aged 35 and above, LTBI screening was not cost-effective, leading to high ICERs and therefore it is not recommended. In line with our findings, the new guidelines of the public health agency of Sweden (from 2020) do not recommend IGRA testing among these individuals as only few would be eligible for treatment. As TPT has higher risk of hepatotoxicity in older persons, the risks might outweigh the benefits. (81) Hesitancy in prescribing preventive treatment for persons above the age of 35 means that it might be more effective to focus on screening for active TB only in this age group. This means discontinuing IGRA screening while replacing it with chest X-ray and perform IGRA only in case of a normal chest X-ray and in presence of additional risk factors for progression, as the public health agency now recommends. (81) This new recommendation by the Public health agency has not been evaluated for its effectiveness or cost effectiveness and further research is needed to have a firm conclusion on the yield and cost per detected case with X-ray screening, compared to for example only symptom screening. The number of persons detected with active TB in our screening cohort was only 12,(84) indicating that many persons would have to be screened for each active case to be detected.

Another influential factor on the CEA results was the country of origin. As predicted from the literature review, the higher the incidence rate of the country of origin, the higher the cost effectiveness of LTBI screening. These findings are in line with the available evidence from other European countries such as Germany and the UK. (185,186) Moreover, a cost-effectiveness study performed by the ECDC covering four countries (Spain, Netherlands, Portugal and Czech Republic) concluded that LTBI screening is cost effective when individuals from very high incidence countries are targeted. (54) The thresholds in these studies varied, however our findings showed that screening individuals from countries with a TB incidence higher than 200/100 000 is cost effective for all individuals younger than 35 years old. Therefore, any recommendations and updated guidelines should take the country of origin into account combined with the age and the risk factors assessment.

Comparing the cost effectiveness analysis results to other studies in other countries is challenging due to difference in modelling approaches and assumptions, as demonstrated by our literature review of methods used in economic evaluations of LTBI screening. Harmonizing the methods of LTBI screening evaluation is a challenge that should be addressed to facilitate cross-country comparisons and policy analyses in the future. The framework for economic modelling of LTBI screening developed as party of this thesis can serve as reference to reduce methodological differences and improve comparability.

Despite the methodological variations, some firm conclusions can be drawn about promising success factors for cost-effective screening that we have uncovered, which are partly at odds with previously published data. High attrition along the LTBI cascade of care was a limiting factor for the cost effectiveness of LTBI screening in several previous economic evaluations of LTBI screening, and much of the attrition has been assumed to be due to lack of patient adherence. This has led ECDC to recommend LTBI screening only when screening programmes can ensure a high screening uptake and treatment initiation. (54) Designing more effective and cost-effective screening entails addressing both patient and provider factors. In the cohort used for our analysis, 97% of patients who were recommended treatment started treatment and among those 91% completed the treatment (84).The high attrition in our data was mainly explained by health workers following the existing guidelines, most importantly the recommendation not to start people over the age of 20 years on treatment unless that had additional risk factors. The potential for further improvements in the care cascade, and thus of cost-effectiveness, seem largely to be in the hands of policy makers and clinicians. There are still some outstanding questions about the age threshold at which the value of providing TPT no longer outweighs the risks. Nevertheless, once there is agreement on which age groups to offer treatments for, our data suggest that patient adherence may not be not be a key challenge in Sweden, and also more generally that patient adherence should be possible to optimize in all countries where this type of screening is offered, given the right supportive health systems structures.

5.2 METHODOLOGICAL CONSIDERATIONS

Qualitative and Mixed-Methods designs

Despite the added value of qualitative research in this thesis, many methodological challenges need to be highlighted. To assess the health examination, participants were recruited from four different settings. However, selection bias may be an issue as the participants who volunteered may misrepresent or have less health needs than the general asylum seeker population in Stockholm. In addition, it was difficult to recruit asylum seekers who had not undergone a health examination in these settings, so no conclusions can be drawn about "no participation". For the mixed-methods study, the subgroup that participated in the interviews are deemed to be representative of LTBI patients in Stockholm due to their socio-demographic characteristic and the recruitment strategy based on the electronic medical records. A concurrent design was applied in this study. An alternative approach would have been to use a sequential design, meaning that the interviewees are chosen based on their EQ-5D and RHS scores. The advantage of sequential design is that it would allow us to interview individuals with worse health status and to deepen the understanding of their needs, but this design can be challenging as it requires contacting some patients and booking an interview time which can be compromised by participant hesitancy and drop-outs.

In addition, interviews were conducted in different languages and translators were used, so there is a possibility that information was lost during the process of translation. However, the main author spoke well in some of the languages and that gave some participants to speak in a language that feel comfortable with thus ensuring they express their experiences easily.

The generalizability of qualitative research findings is another challenge, and we acknowledge that our results may not be applicable for asylum seekers in other parts of Sweden. However, our results are in line with the available evidence from studies in other Swedish counties.

HRQOL

HRQoL of TB and LTBI patients can be measured by using different instruments. The choice of EQ-5D-3L for this study was mainly based on the availability of the instrument in the needed languages, However, as discussed above EQ-5D-5L could be a more suitable and sensible instrument, or alternatively SF-36. There is no gold standard for measuring HRQoL among TB patients and the available studies vary widely in the variety and analysis of results.

For our analyses, the EQ-5D-3L responses were used to generate utility scores. The choice of value set is a challenge as the asylum seekers come from different countries and constitute a very heterogenous cohort from different countries. In study III, the LTBI cohort was compared to the general population of Stockholm. Using the Swedish experience-based value set was the ideal choice to use among the Stockholm cohort. Therefore, to allow comparison between the two groups, the same value set was used to generate the utility of score of LTBI patients. As a sensitivity analysis, the UK hypothetical value set was used and generated very similar results with the same median and 75th percentile, being 1, and a slightly higher 25th percentile (0,83 instead of 0,79).

For the active TB cohort who are foreign-born, there was no reason to believe that the Swedish experience-based value set is an appropriate choice, so the UK hypothetical value set was used instead as it facilitates comparison with future studies. As a sensitivity analysis, the Swedish experienced-based value was used and generated a mean utility score of 0,77 at the beginning of the treatment which increased to 0,91 by the end of the treatment, a statistically significant difference with a p-value < 0,001. The higher values generated through the Swedish experienced based value set were expected as shown in a study comparing the two value sets.(187) Comparison with the LTBI cohort lead to a statistically significant difference regardless of the value set choice.

Economic modelling

Despite being based on a real-life cascade of care data, the economic analysis has many methodological limitations due to the simplification of the model and the assumptions used in terms of epidemiological parameters.

The model developed through this thesis is a Markov model and therefore it is not a transmission model that can accommodate for transmission of infection among individuals.

In addition, the model could have overestimated the cost effectiveness of LTBI screening through the following assumptions and simplifications: 1) not including the costs of potential

ADR and its impact on treatment adherence; 2) assuming a 100% sensitivity of IGRA which does not represent the real-life situation and; 3) assuming a 100% efficacy of TB treatment.

To simplify the model, another assumption was made in terms of standardizing the reactivation rate of LTBI for all patients regardless of their age, risk factors and time since infections, even though these factors are shown to impact the risk of reactivation. We did not have data on time since infection or risk factor profile of the screened persons so could not include these in the model.

5.3 IMPLICATIONS

The results of this thesis can lead to some recommendations summarized below:

- Health examinations are a suitable way to screen asylum seekers for infectious diseases, including TB and LTBI. However, they should be used as an opportunity to address the health needs of asylum seekers through a holistic approach that goes beyond infectious disease control.

- Asylum seekers diagnosed with LTBI need better information in order to raise awareness about the disease and address misconceptions and stigma related to TB disease. Mental health care can be part of LTBI management if patients seem worried and if the diagnosis compromised their quality of life and well-being.

- TB patients in Stockholm have a compromised HRQoL and a decrement of 0,28 was calculated through this thesis. This estimate can be used in other health economic models for similar epidemiological and demographic settings. However, future research using EQ-5D-5L or SF-36 might be valuable to validate or finetune the results of this work.

- LTBI screening should only be performed when the individuals are eligible for TPT, otherwise screening is not cost-effective, and it can be unethical and even compromise mental health of asylum seekers by creating unnecessary worry and stigmatization.

- LTBI screening followed by initiation of TPT in Stockholm is cost-effective and recommended for individuals under the age of 35. For older patients, the current LTBI screening strategy is not recommended. The alternative strategy of chest X-ray screening followed by IGRA screening is not evaluated and future research is needed to assess the cost-effectiveness of this approach.

6 CONCLUSIONS

LTBI screening among asylum seekers in Stockholm is cost-effective in adolescents, while it is moderately cost-effective in children under the age of 13 and in the age group 20 to 34. The moderate cost-effectiveness in the age group 20 to 34 is mainly due to the restrictive practices of offering treatment for persons over the age of 20 years. The cascade of care indicators affected the cost-effectiveness analysis results to a large extent, mainly in terms of the proportion being referred and offered treatment. Therefore, screening should only be recommended for asylum seekers who are potentially eligible for treatment.

Our findings show that TB disease can affect the physical, psychological and social well-being of asylum seekers substantially. Mental health concerns are prominent among LTBI patients who are asylum seekers or refugees, but this is probably more due to migration-related factors than to LTBI. Nevertheless, there is a need for a holistic approach to TB and LTBI-care among this vulnerable group, including mental health support and improved systems for communicating information to address the concerns of patients, clarify the differences between TB and LTBI, and decrease the stigma around TB disease.

Uncertainties, fears and misconceptions among asylum seekers are not limited to LTBI diagnosis and they should be addressed earlier during the health examinations regardless of the LTBI status. Health examination is acceptable, accessible and affordable according to asylum seekers. However, its quality and perceived value can be compromised if its focus is predominantly on infectious diseases and neglect of the other health needs.

7 ACKNOWLEDGEMENTS

It has been an incredible journey of learning and evolving as a person and as a researcher. There are many people I would like to thank, and I will try to summarize my thoughts in words, however my gratitude towards the people around me goes beyond these written words.

I will start where it all started, the family I was born to. **Mom, dad, grandma, aunt, brother and sister**- thank you for your unconditional love and support, I dedicate this success to you, and I hope that I always make you proud.

Second, it's the family I chose. **Lucy, JoJo, Hong and Katja**, thank you for being there from the start of this journey, you supported my success, failure and growth in many incredible ways, I am a lucky person to have you around. And of course, **Rod**, Obrigado! for everything and all what you handle while living with me, can't imagine these years without you in my life. **Katie and Faris-** you have been there since the very early stage; we had our falls (even between the train rails) thanks for all the support and help. **Jhady, Clem, Stefan, Oriol,** thanks for all the good times and laughs even in the darkest moments. **James,** thanks for your encouragement and "realistic" advices. And to the beautiful souls, **Natalie, Tannaz, Geno, Pardis, Amari and Paulina,** thank you for the incredible moments that we shared and for being an amazing source of comfort and love even in the hardest times.

The family is big, and part of it is the Irish family. **Euan**, thanks for introducing me to amazing people and being a thoughtful friend. **Ulrika** thanks for being an incredible person and for your language check help (and the amazing books I stole). **Han, Jess, Hil, Fiona, Cait, Libby**- thanks for incredible memories (most of them are tipsy but unforgettable)

Sara, thank you for being an amazing and supportive friend and academic partner, since our master thesis until now, so happy to see your success in different ways. **Ana and Elena**, thanks for your support and advices and warm hearts. **Megan** thanks for the amazing time and chats we have as office neighbors. **Lisa**, thanks for all the memories we shared inside and outside the office and for chairing my defence. **Renee**, thanks for being my mentor and for the laughs we had in the kitchen. **Olivia and Kristi**, thanks for being incredible colleagues and for your encouragement, I hope to work with you in the future. You all made this journey smoother and more fun.

I would like to thank **Fredrik Norström**, the opponent of the defence, as well as the examination board members, **Malin Inghammar, Peter Lindgren, Bernadette Kumar**, for putting time and effort in reading my thesis and giving me feedback. I am grateful for your contribution.

Big thank you for my supervisors, **Asli Kulane** who has always being a positive supportive person, your kindness always brings calm. **Andrew Siroka**, thank you for your help and

advices, and good luck with your work. **Charlotte Deogan**, your encouraging words and valuable feedback are always appreciated and thank you for your help throughout this process.

I would like to thank the colleagues at the TB clinic at Karolinska Hospital, **Judith Bruchfeld, Lena Jansson and the nurses of the clinic** for all the support in conducting the research. **Joanna Nederby Öhd, Maria Pia Hergens and Jerker Jonsson**, thanks for your contribution to the work of this thesis. **Cecilia Magnusson**, thank you for your continuous encouragement and support.

Finally, all of this won't take place and I would have never thought of an academic career if it wasn't for my main supervisor **Knut Lönnroth**. Thank you for believing in me from the start and giving me so many opportunities. Your professionalism and dedication to your work are inspiring, and your ethics and human values are even a bigger inspiration. It has been an honor to work with you and learn from every feedback, every suggestion and every discussion. My sincere gratitude for your mentorship and support!

8 REFERENCES

1. Sakula A. Robert Koch: Centenary of the discovery of the tubercle bacillus, 1882. Bull Int Union Tuberc. 1982;57(2):111–6.
2. Glaziou P, Sismanidis C, Floyd K, Raviglione M. Global epidemiology of tuberculosis. Cold Spring Harb Perspect Med. 2015;5(2).
3. Riley R. The contagiosity of tuberculosis. Schweiz Med Wochenschr. 1983;113(3):75–9.
4. Smith I. Mycobacterium tuberculosis Pathogenesis and Molecular. Clin Microbiol Rev [Internet]. 2003;16(3):463–96. Available from: http://cmr.asm.org/cgi/content/abstract/16/3/463
5. Heemskerk D, Caws M, Marais B, Farrar J. Tuberculosis in Adults and Children. Springer Briefs in Public Health. 2015.
6. Solovic I, Jonsson J, Korzeniewska-Kosela M, Chiotan DI, Pace-Asciak A, Slump E, et al. Challenges in diagnosing extrapulmonary tuberculosis in the European Union, 2011. Eurosurveillance. 2013;18(12):1–9.
7. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of Extrapulmonary Tuberculosis in the United States, 1993–2006. Clin Infect Dis. 2009;49(9):1350–7.
8. Duarte R, Lönnroth K, Carvalho C, Lima F, Carvalho ACC, Muñoz-Torrico M, et al. Tuberculosis, social determinants and co-morbidities (including HIV). Pulmonology. 2018;24(2):115–9.
9. World Health Organization. Global Tuberculosis Report 2020. Geneva; 2020.
10. World Health Organisation. Tuberculosis and HIV [Internet]. World Health organisation. 2020 [cited 2020 Apr 27]. Available from: https://www.who.int/hiv/topics/tb/en/
11. Bruchfeld J, Correia-Neves M, Kallenius G. Tuberculosis and HIV coinfection. Cold Spring Harb Perspect Med. 2015;5(7):1–15.
12. Franco I, Sousa P, Gomes M, Oliveira A, Gaio AR, Duarte R. Social profile of the highest tuberculosis incidence areas in Portugal. Rev Port Pneumol . 2016;22(1):50–2.
13. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. Soc Sci Med. 2009;68(12):2240–6.
14. Centre for Disease Prevention and Control. Treatment for TB Disease. 2020.
15. Sotgiu G, Centis R, D'Ambrosio L, Battista Migliori G. Tuberculosis treatment and drug regimens. Cold Spring Harb Perspect Med. 2015;5(5):1–12.
16. Rabahi M, da salvia J, Ferreira AC, Taunus-Silva D, Conde M. Tuberculosis Treatment. Soc Bras Pneumol e Tisiol. 2016;43(5):472–86.
17. Getahun H, Matteelli A, Abubakar I, Abdel Aziz M, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46(6):1563–76.
18. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016;13(10):1–13.
19. Moran-Mendoza O, MARION S, Elwood K, PATRICK D, FitzGerald JM. Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. Int J Tuberc lung Dis. 2010;14(9):1112–9.
20. Horsburgh CRJ, O'Donnell M, Chamblee S, Moreland JL, Johnson J, Marsh BJ, et al.

Revisiting rates of reactivation tuberculosis: a population-based approach. Am J Respir Crit Care Med. 2010 Aug;182(3):420–5.
21. Mun L, Stagg HR, Abubakar I. Diagnosis and Management of Latent Tuberculosis Infection. Cold Spring Harb Perspect Med. 2015;5:1–13.
22. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: Latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009;33(5):956–73.
23. World Health organisation. Global tuberculosis report 2018. 2018.
24. World Health Organisation. Global Tuberculosis Report 2019. Geneva;
25. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet. 2015;385(9979):1799–801.
26. WHO. Framework towards tuberculosis elimination in low-incidence countries. geneva; 2014.
27. Kamper-Jorgensen Z, Andersen AB, Kok-Jensen A, Kamper-Jorgensen M, Bygbjerg IC, Andersen PH, et al. Migrant tuberculosis: the extent of transmission in a low burden country. BMC Infect Dis [Internet]. 2012;12:60. Available from: http://www.biomedcentral.com/1471-2334/12/60%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012251667%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/22423983
28. Jonsson J, Hoffner S, Berggren I, Bruchfeld J, Ghebremichael S, Pennhag A, et al. Comparison between RFLP and MIRU-VNTR genotyping of mycobacterium tuberculosis strains isolated in stockholm 2009 to 2011. PLoS One. 2014;9(4).
29. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, De Vries G, Diel R, et al. Towards tuberculosis elimination: An action framework for low-incidence countries. Eur Respir J. 2015;45(4):928–52.
30. Ricks PM, Cain KP, Oeltmann JE, Kammerer JS, Moonan PK. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. PLoS One. 2011;6(11):2005–9.
31. World Health Organisation. The 10 Essential Public Health Operations [Internet]. [cited 2020 Sep 1]. Available from: https://www.euro.who.int/en/health-topics/Health-systems/public-health-services/policy/the-10-essential-public-health-operations
32. World Health Organization. Implementing the WHO stop TB strategy. WHO Libr Cat. 2008;
33. Carter DJ, Glaziou P, Lönnroth K, Siroka A, Floyd K, Weil D, et al. The impact of social protection and poverty elimination on global tuberculosis incidence: a statistical modelling analysis of Sustainable Development Goal 1. Lancet Glob Heal. 2018;6(5):e514–22.
34. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: Systematic review and meta-analysis. BMJ [Internet]. 2014;349(August):1–11. Available from: http://dx.doi.org/doi:10.1136/bmj.g4643
35. Moliva JI, Turner J, Torrelles JB. Prospects in Mycobacterium bovis Bacille Calmette et Guérin (BCG) vaccine diversity and delivery: Why does BCG fail to protect against tuberculosis? Vaccine [Internet]. 2015;33(39):5035–41. Available from: http://dx.doi.org/10.1016/j.vaccine.2015.08.033
36. Nathavitharana RR, Lederer P, Tierney DB, Nardell E, Israel B, Medical D. Treatment as Prevention and Other Interventions to Decrease MDR-TB Transmission.

2019;23(4):396–404.
37. Lönnroth K, Mor Z, Bruchfeld J, Erkens C, Nathavitharana R, van der Werf M LC. TB in immigrants from endemic to low-incidence countries –epidemiology, determinants and intervention options. Int J Tuberc Lung Dis. 2017;
38. WHO. Systematic screening for active tuberculosis. 2013;1–146.
39. Ankrah AO, Glaudemans AWJM, Maes A, Van de Wiele C, Dierckx RAJO, Vorster M, et al. Tuberculosis. Semin Nucl Med. 2018;48(2):108–30.
40. Ayub A, Yale SH, Reed KD, Nasser RM, Gilbert SR. Testing for latent tuberculosis. Clin Med Res. 2004;2(3):191–4.
41. Al-Orainey IO. Diagnosis of latent tuberculosis: Can we do better? Ann Thorac Med. 2009 Jan;4(1):5–9.
42. Pai M, Denkinger CM, Kik S V., Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014;27(1):3–20.
43. Takasaki J, Manabe T, Morino E, Muto Y, Hashimoto M, Iikura M, et al. Sensitivity and specificity of QuantiFERON-TB Gold Plus compared with QuantiFERON-TB Gold In-Tube and T-SPOT.TB on active tuberculosis in Japan. J Infect Chemother [Internet]. 2018;24(3):188–92. Available from: https://doi.org/10.1016/j.jiac.2017.10.009
44. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A Systematic Review on TST and IGRA Tests Used for Diagnosis of LTBI in Immigrants. Mol Diagnosis Ther. 2015;19(1):9–24.
45. Erkens CGM, Dinmohamed AG, Kamphorst M, Toumanian S, Van Nispen-Dobrescu R, Alink M, et al. Added value of interferon-gamma release assays in screening for tuberculous infection in the Netherlands. Int J Tuberc Lung Dis [Internet]. 2014;18(4):413–20. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372723601
46. World Health organisation. Latent tuberculosis infection - Updated and consolidated guidelines for programmatic management. 2018.
47. Kim HW, Kim JS. Treatment of Latent Tuberculosis Infection and Its Clinical Efficacy Why Treatment of LTBI Is Important. Tuberc Respir Dis (Seoul). 2018;3536:6–12.
48. Huang Y-W, Yang S-F, Yeh Y-P, Tsao TC-Y, Tsao S-M. Impacts of 12-dose regimen for latent tuberculosis infection. Medicine (Baltimore). 2016;95(34):e4126.
49. Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: A prospective cohort study. Drug Healthc Patient Saf [Internet]. 2014;6:145–9. Available from: http://www.dovepress.com/getfile.php?fileID=22116%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015214031
50. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. J Clin Exp Hepatol [Internet]. 2013;3(1):37–49. Available from: http://dx.doi.org/10.1016/j.jceh.2012.12.001
51. Wheeler C, Mohle-Boetani J. Completion Rates, Adverse Effects, and Costs of a 3-Month and 9-Month Treatment Regimen for Latent Tuberculosis Infection in California Inmates, 2011-2014. Public Health Rep. 2019;134(1_suppl):71S-79S.
52. McClintock AH, Eastment MK, McKinney CM, Pitney CL, Narita M, Park DR, et al. Treatment completion for latent tuberculosis infection: A retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC Infect Dis. 2017;17(1):1–8.
53. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, Van Der Werf MJ. Treatment of latent tuberculosis infection: An updated network meta-analysis. Ann Intern Med.

2017;167(4):248–55.
54. ECDC (European Centre for Disease Prevention and Control). Cost-effectiveness analysis of programmatic screening strategies for latent tuberculosis infection in the EU/EEA [Internet]. 2018. Available from: www.ecdc.europa.eu
55. Sironi A, Bauloz C, Emmanuel M. INTERNATIONAL MIGRATION LAW Glossary on Migration. Int Organ Migr. 2019;224.
56. OECD. International Migration Outlook 2019. paris; 2019.
57. International Organization for Migration. World Migration Report 2020 [Internet]. International Organization For Migration. Geneva; 2019. Available from: https://reliefweb.int/report/world/world-migration-report-2020
58. UNHCR. Refugee Facts [Internet]. Available from: https://www.unrefugees.org/refugee-facts/what-is-a-refugee/
59. United Nations- Department of Economic and Social Affairs. International Migration 2019 Report. Handbook of Sociology and Human Rights, International Population Division (2019). (ST/ESA/SER.A/438). 2019. 300–307 p.
60. Puchner K, Karamagioli E, Pikouli A, Tsiamis C, Kalogeropoulos A, Kakalou E, et al. Time to rethink refugee and migrant health in europe: Moving from emergency response to integrated and individualized health care provision for migrants and refugees. Int J Environ Res Public Health. 2018;15(6).
61. Dhavan P, Dias HM, Creswell J, Weil D. An overview of tuberculosis and migration. Int J Tuberc Lung Dis. 2017;21(6):610–23.
62. Lönnroth K, Mor Z, Bruchfeld J, Erkens C, Nathavitharana R, van der Werf M LC. Addressing TB in immigrants from endemic to low-incidence countries – rationale, epidemiology, determinants and intervention options. Int J Tuberc Lung Dis. 2017;21(6).
63. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Med. 2016;14:48.
64. Rendon A, Centis R, Zellweger JP, Solovic I, Torres-Duque CA, Robalo Cordeiro C, et al. Migration, TB control and elimination: Whom to screen and treat. Pulmonology [Internet]. 2018;24(2):99–105. Available from: http://dx.doi.org/10.1016/j.rppnen.2017.11.007
65. Sandgren A, Schepisi MS, Sotgiu G, Huitric E, Migliori GB, Manissero D, et al. Tuberculosis transmission between foreign- and native-born populations in the EU/EEA: A systematic review. Eur Respir J. 2014;43(4):1159–71.
66. Lonnroth K, Mor Z, Erkens C, Bruchfeld J, Nathavitharana RR, van der Werf MJ, et al. Tuberculosis in migrants in low-incidence countries: epidemiology and intervention entry points. Int J Tuberc Lung Dis. 2017;21(6):624–37.
67. Odone A, Tillmann T, Sandgren A, Williams G, Rechel B, Ingleby D, et al. Tuberculosis among migrant populations in the European Union and the European Economic Area. Eur J Public Health. 2015;25(3):506–12.
68. European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2020. 2020.
69. Collin SM, De Vries G, Lönnroth K, Migliori GB, Abubakar I, Anderson SR, et al. Tuberculosis in the European Union and European economic Area: A survey of national tuberculosis programmes. Eur Respir J [Internet]. 2018;52(6). Available from: http://dx.doi.org/10.1183/13993003.01449-2018
70. Dobler CC, Fox GJ, Douglas P, Viney KA, Khan FA, Temesgen Z, et al. Screening for tuberculosis in migrants and visitors from high-incidence settings: Present and future

perspectives. Eur Respir J [Internet]. 2018;52(1). Available from: http://dx.doi.org/10.1183/13993003.00591-2018
71. Dobler CC. Screening strategies for active tuberculosis: Focus on cost-effectiveness. Clin Outcomes Res. 2016;8:335–47.
72. Collin SM, Wurie F, Muzyamba MC, de Vries G, Lönnroth K, Migliori GB, et al. Effectiveness of interventions for reducing TB incidence in countries with low TB incidence: A systematic review of reviews. Eur Respir Rev [Internet]. 2019;28(152). Available from: http://dx.doi.org/10.1183/16000617.0107-2018
73. Ködmön C, Zucs P, van der Werf MJ. Migration-related tuberculosis: Epidemiology and characteristics of tuberculosis cases originating outside the European Union and European Economic Area, 2007 to 2013. Eurosurveillance. 2016;21(12):1–10.
74. Linas BP, Wong AY, Freedberg KA, Horsburgh CRJ. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med. 2011 Sep;184(5):590–601.
75. Zenner D, Hafezi H, Potter J, Capone S MA. Effectiveness and cost-effectiveness of screening migrants for active and latent TB – a narrative review of the evidence. Int J Tuberc Lung Dis. 2018;23(14).
76. Kunst H, de Vries G et al. TB screening in immigrants in Europe – Comparative analysis of policies, surveillance systems and results. Int J Tuberc Lung Dis. 2017;21(8).
77. Kunst H, Burman M, Arnesen TM, Fiebig L, Hergens M-P, Kalkouni O, et al. Tuberculosis and latent tuberculous infection screening of migrants in Europe: comparative analysis of policies, surveillance systems and results. Int J Tuberc Lung Dis [Internet]. 2017;21(8):840–51. Available from: http://www.ingentaconnect.com/content/10.5588/ijtld.17.0036
78. The Public health agency of Sweden. Tuberulosis [Internet]. 2020. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/sjukdomsstatistik/tuberkulos/?p=48740
79. Pedersen MK, Lillebaek T, Andersen AB, Soini H, Haanperä M, Groenheit R, et al. Trends and differences in tuberculosis incidences and clustering among natives in Denmark, Sweden and Finland: comparison of native incidences and molecular epidemiology among three low-incidence countries. Clin Microbiol Infect. 2018;24(7):717–23.
80. Swedish Public health agency. Recommendations for preventive measures against tuberculosis. Stockholm; 2017.
81. The Public health agency of Sweden. recommendations for preventive measures against Tuberculosis. 2020;
82. Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: A national, primary care-based cohort and self-controlled case series study. Am J Respir Crit Care Med. 2012;185(7):779–84.
83. Jonsson J, Kühlmann-Berenzon S, Berggren I, Bruchfeld J. Increased risk of active tuberculosis during pregnancy and postpartum: A register-based cohort study in Sweden. Eur Respir J [Internet]. 2020;55(3). Available from: http://dx.doi.org/10.1183/13993003.01886-2019
84. Nederby-Öhd J, Hergens M, Buxmaum C, Shedrawy J, Bruchfeld J, Lönnroth K. Assessment of the care cascade of latent tuberculosis screening and treatment for asylum seekers in Stockholm, Sweden 2015-2018 - a record linkage study. Eur Respir J. 2020;
85. Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, et al. Latent Tuberculosis

Infection Screening in Immigrants to Low-Incidence Countries : A Meta-Analysis. Mol Diagn Ther [Internet]. 2015;107–17. Available from: http://dx.doi.org/10.1007/s40291-015-0135-6
86. the Swedish government. Lag om hälso- och sjukvård åt asylsökande m.fl. (Law on healthcare for asylum seekers and others). SFS 2008:344.
87. Stockholm County Council. Lag om hälso- och sjukvård åt asylsökande m. fl. (SFS 2008:344). [Law on healthcare for asylum seekers] Stockholm: Justitiedepartementet L7; 2008-05-22. [Cited 2017-01-16]. Available in Swedish at https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk.
88. Stockholm County Council. Stockholm County Council. Hälsoundersökning för asylsökande. [Health examination for asylum seekers] Stockholm: Britta Manninen; 2016 [2016-11-21; cited 2017-05-03]. Available in Swedish from: http://www.vardgivarguiden.se/patientadministration/patientavg.
89. National Board of Health and Welfare. SOSFS 2011:11 Socialstyrelsens föreskrifter och allmänna råd om hälsoundersökning av asylsökande (National Board of Health and Welfare Regulations and General advice on health investigation of asylum seekers) [Internet]. 2013 [cited 2017 May 12]. Available from: http://www.socialstyrelsen.se/sosfs/2011-11
90. Delilovic S, Åsbring N, Hergens M, Kulane A, Martilla A, Nederby-Öhd J, et al. Hälsoundersökningar för asylsökande och nyanlända – vägen fram Aktörers , vårdgivares och migranters perspektiv. 2017.
91. Lindkvist P, Johansson EVA. A state of limbo – in transition between two contexts : Health assessments upon arrival in Sweden as perceived by former Eritrean asylum seekers. 2015;48(5):548–558.
92. Pacheco LL, Jonzon R, Hurtig A. Health Assessment and the Right to Health in Sweden : Asylum Seekers ' Perspectives. 2016;1–15.
93. Delilovic S, Kulane A, Åsbring N, Marttila A, Lönnroth K. What value for whom ? – provider perspectives on health examinations for asylum seekers in Stockholm , Sweden. BMC Health Serv Res. 2018;1–9.
94. Wångdahl J, Westerling R, Lytsy P, Mårtensson L. Perspectives on health examination for asylum seekers in relation to health literacy-focus group discussions with Arabic and Somali speaking participants. BMC Health Serv Res. 2019;19(1):1–12.
95. Wångdahl J, Lytsy P, Mårtensson L, Westerling R. Health literacy and refugees' experiences of the health examination for asylum seekers - A Swedish cross-sectional study Health behavior, health promotion and society. BMC Public Health [Internet]. 2015;15(1). Available from: http://dx.doi.org/10.1186/s12889-015-2513-8
96. Su Y, Garcia Baena I, Harle AC, Crosby SW, Micah AE, Siroka A, et al. Tracking total spending on tuberculosis by source and function in 135 low-income and middle-income countries, 2000–17: a financial modelling study. Lancet Infect Dis [Internet]. 2020;20(8):929–42. Available from: http://dx.doi.org/10.1016/S1473-3099(20)30124-9
97. Russells S. Economic burden of illness for household in developing countries: a review of studies focusing on malaria, tuberculosis and human immunodeficiency virus /acquired immunodeficiency syndrome. Am J Trop Med Hyg [Internet]. 2004;71(Suppl 2):147–55. Available from: https://www.ncbi.nlm.nih.gov/books/NBK3768/pdf/Bookshelf_NBK3768.pdf
98. Tanimura T, Jaramillo E, Weil D, Raviglione M, L??nnroth K. Financial burden for tuberculosis patients in low- And middle-income countries: A systematic review. Eur Respir J. 2014;43(6):1763–75.

99. Diel R, Vandeputte J, De Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: A systematic analysis and cost calculation. Eur Respir J. 2014;43(2):554–65.
100. Wada PY, Lee-Rodriguez C, Hung YY, Skarbinski J. Burden of active tuberculosis in an integrated health care system, 1997-2016: Incidence, mortality, and excess health care utilization. Open Forum Infect Dis. 2020;7(1):1–5.
101. Shete PB, Reid M, Goosby E. Message to world leaders: we cannot end tuberculosis without addressing the social and economic burden of the disease. Lancet Glob Heal [Internet]. 2018;6(12):e1272–3. Available from: http://dx.doi.org/10.1016/S2214-109X(18)30378-4
102. Viney K, Islam T, Hoa NB, Morishita F, Lönnroth K. The financial burden of tuberculosis for patients in the Western-Pacific region. Trop Med Infect Dis. 2019;4(2):1–12.
103. Kik S V, Olthof SPJ, de Vries JTN, Menzies D, Kincler N, van Loenhout-Rooyakkers J, et al. Direct and indirect costs of tuberculosis among immigrant patients in the Netherlands. BMC Public Health. 2009;9:283.
104. Pedrazzoli D, Borghi J, Viney K, Houben RMGJ, Lönnroth K. Measuring the economic burden for TB patients in the end TB strategy and universal health coverage frameworks. Int J Tuberc Lung Dis. 2019;23(1):5–11.
105. Kirigia JM, Muthuri RDK. Productivity losses associated with tuberculosis deaths in the World Health Organization African region. Infect Dis Poverty [Internet]. 2016;5(1):1–12. Available from: http://dx.doi.org/10.1186/s40249-016-0138-5
106. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: Monitoring Health and Social Protection Coverage in the Context of Tuberculosis Care and Prevention. PLoS Med. 2014;11(9).
107. Adeyi O, Darley S, Floyd K, Dye C, Klein E, Laxminarayan R. Economic benefit of Tuberculosis control. 2007;4295(August):1–59. Available from: http://syracuse.summon.serialssolutions.com/link/0/eLvHCXMwY2BQSLY0SE42TzQxTEoyN0tJs0i1SAU2KtIsLIAixkbgW-f8Ak09fMydAyxdkEpzN1EGGTfXEGcPXfBpoUmJednxBYkFwGZQPLDUNDUUY2ABdolTAWlcGBs
108. Floyd K, Hutubessy R, Kliiman K, Centis R, Khurieva N, Jakobowiak W, et al. Cost and cost-effectiveness of multidrug-resistant tuberculosis treatment in Estonia and Russia. Eur Respir J. 2012;40(1):133–42.
109. Rajbhandary S, Marks S, Bock N. Costs of patients hospitalized for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8(8):1012–6.
110. Drummond M, Skulther M, Torrance G, O`brien B, Stoddart G. methods for economic evaluations of health care programmes. 3rd ed. New York: Oxford University Press (maker); 2005.
111. Kernick D. An introduction to the basic principles of health economics for those involved in the development and delivery of headache care. Cephalalgia. 2005;25(9):709–14.
112. Drummond M, Sculpher M. Common methodological flaws in economic evaluations. Med Care [Internet]. 2005;43(7 Suppl):5–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16056003
113. Briggs,Andrew Claxton,Karl Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press (maker); 2006.
114. Auguste P, Tsertsvadze A, Court R, Pink J. A systematic review of economic models used to assess the cost-effectiveness of strategies for identifying latent tuberculosis in

high-risk groups. Tuberculosis [Internet]. 2016;99:81–91. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L610387472
115. Zammarchi L, Casadei G, Strohmeyer M, Bartalesi F, Liendo C, Matteelli A, et al. A scoping review of cost-effectiveness of screening and treatment for latent tubercolosis infection in migrants from high-incidence countries. BMC Health Serv Res [Internet]. 2015;15:412. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26399233%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4581517
116. Campbell JR, Sasitharan T, Marra F. A Systematic Review of Studies Evaluating the Cost Utility of Screening High-Risk Populations for Latent Tuberculosis Infection. Appl Health Econ Health Policy. 2015 Aug;13(4):325–40.
117. the Swedish Dental and Pharmaceutical Benefits Agency (TLV). The Pharmaceutical Benefits Board's general advice (Läkemedelsförmånsnämndens allmänna råd). 2003;LFNAR 2003:2.
118. Hannah A, Dick M. Identifying gaps in the quality of latent tuberculosis infection care. J Clin Tuberc Other Mycobact Dis [Internet]. 2020;18:100142. Available from: https://doi.org/10.1016/j.jctube.2020.100142
119. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: A systematic review and meta-analysis. Lancet Infect Dis. 2016;1269–78.
120. Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. BMC Infect Dis [Internet]. 2016;16:204. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27184748%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4869320
121. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34(7):645–9.
122. Felce D, Perry J. Quality of life: Its definition and measurement. Res Dev Disabil. 1995;16(1):51–74.
123. Whitehead SJ, Ali S. Health outcomes in economic evaluation: The QALY and utilities. Br Med Bull. 2010;96(1):5–21.
124. Azoulay É, Kentish-Barnes N, Pochard F. Health-related quality of life: An outcome variable in critical care survivors. Chest. 2008;133(2):339–41.
125. Fayers P, Machin D. Quality of Life: The Assessment, Analysis and Interpretation of Patient-reported Outcomes. 2nd ed. John Wiley & Sons; 2013.
126. Rabin R, De Charro F. EQ-5D: A measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337–43.
127. Group TE. EuroQol * - a new facility for the measurement of health-related quality of life. 1990;16:199–206.
128. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001;33(5):350–7.
129. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in orthopaedics: A brief guide. J Bone Jt Surg - Am Vol. 2014;97(19):1628–34.
130. Aggarwal AN. Quality of life with tuberculosis. J Clin Tuberc Other Mycobact Dis [Internet]. 2019;17:100121. Available from: https://doi.org/10.1016/j.jctube.2019.100121
131. Diel R, Lampenius N. Cost-effectiveness analysis of interventions for tuberculosis

control: DALYs versus QALYs. Pharmacoeconomics. 2014;32(7):617–26.
132. Guo N, Marra F, Marra CA. Measuring health-related quality of life in tuberculosis: a systematic review. Health Qual Life Outcomes [Internet]. 2009;7(1):14. Available from: http://hqlo.biomedcentral.com/articles/10.1186/1477-7525-7-14
133. Newbold KB, Danforth J. Health status and Canada ' s immigrant population. Soc Sci Med. 2003;57:1981–95.
134. Zheng Wu, Penning M, Schimmele CM. Immigrant Status and Unmet Health Care Needs. Can J public Heal. 2005;369–73.
135. Hansel NN, Wu AW, Chang B, Diette GB. Quality of life in tuberculosis: Patient and provider perspectives. Qual Life Res. 2004;13(3):639–52.
136. Bauer M, Ahmed S, Benedetti A, Greenaway C, Lalli M, Leavens A, et al. Health-related quality of life and tuberculosis : a longitudinal cohort study. Health Qual Life Outcomes. 2015;13(65):1–13.
137. Jansson L, Shedrawy J, Knut L, Bruchfeld J, Kulane A. Latent tuberculosis in pregnant women: a patient perspective. Int J Tuberc Lung Dis. 2019;
138. Jamshed S. Qualitative research method - interviewing and observation. 2014;5(4):4–5.
139. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: Concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105–12.
140. United Nations Committee on Economics Social and Cultural rights. The Right to the Highest Attainable Standard of Health. Vol. 2000. 2000.
141. Check J, Schutt RK. Research methods in education. Sage Publications; 2012. 159–185 p.
142. Curry LA, Krumholz HM, O'Cathain A, Clark VLP, Cherlin E, Bradley EH. Mixed methods in biomedical and health services research. Circ Cardiovasc Qual Outcomes. 2013;6(1):119–23.
143. Caruana EJ, Roman M, Hernández-Sánchez J, Solli P. Longitudinal studies. J Thorac Dis. 2015;7(11):E537–40.
144. Katz M. Study Design and statistical analysis: A Practical Guide for Clinicians. Cambridge; 2006.
145. Stockholm County Council. Hälsa Stockholm 2014. stockholm; 2014.
146. Hollifield M, Verbillis-Kolp S, Farmer B, Toolson EC, Woldehaimanot T, Yamazaki J, et al. The Refugee Health Screener-15 (RHS-15): Development and validation of an instrument for anxiety, depression, and PTSD in refugees. Gen Hosp Psychiatry. 2013;35(2):202–9.
147. Martínez-Mesa J, González-Chica DA, Duquia RP, Bonamigo RR, Bastos JL. Sampling: How to select participants in my research study? An Bras Dermatol. 2016;91(3):326–30.
148. Wheeldon J, Ahlberg MK. Mapping Mixed-Methods Research: Theories, Models and Measures. Vis Soc Sci Res. 2012;113–48.
149. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs - Principles and practices. Health Serv Res. 2013;48(6 PART2):2134–56.
150. Cherepanov D, Palta M, Fryback D. Underlying dimensions of the five health related Quality of Life measures used in utility assessment. Med Care. 2013;48(8):718–25.
151. Guetterman TC, Fetters MD, Creswell JW. Integrating Quantitative and Qualitative Results in Health Science Mixed Methods Research Through Joint Displays. Ann Fam Med. 2015;13(6):554–61.
152. Swedish Tax Agency (Skatteverket). Employer contributions (Arbetsgivaravgifter).

Available from:
https://www.skatteverket.se/foretagorganisationer/arbetsgivare/socialavgifter/arbetsgivaravgifter.4.233f91f71260075abe8800020817.html
153. Statistics Sweden (SCB). Wage distribution by sector and gender 2016 (Lönespridning efter sektor och kön 2016) [Internet]. Available from: http://www.scb.se/hitta-statistik/statistik-efter-amne/arbetsmarknad/loner-och-arbetskostnader/lonestrukturstatistik-hela-ekonomin/pong/tabell-och-diagram/lonespridning-efter-sektor-och-kon/
154. Nkulu Kalengayi FK, Hurtig AA-KA-K, Nordstrand A, Ahlm C, Ahlberg BMB, LI P, et al. Perspectives and experiences of new migrants on health screening in Sweden. BMC Health Serv Res [Internet]. 2015;16(1):14. Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-015-1218-0
155. Shickle D, Chadwick R. The ethics of screening: Is "screeningitis" an incurable disease? J Med Ethics. 1994;20(1):12–8.
156. Bozorgmehr K, Razum O. Effect of restricting access to health care on health expenditures among asylum-seekers and refugees: A quasi-experimental study in Germany, 1994-2013. PLoS One. 2015;10(7):1994–2013.
157. Bozorgmehr K, Wahedi K, Noest S, Szecsenyi J, Razum O. Infectious disease screening in asylum seekers: Range, coverage and economic evaluation in Germany, 2015. Eurosurveillance. 2017;22(40).
158. Legido-Quigley H, Prof NP, Tan ST, Pajin L, Suphanchaimat R, Wickramage K, et al. Healthcare is not universal if undocumented migrants are excluded. BMJ. 2019;366.
159. Trummer U, Novak-Zezula S, Renner A-T, Wilczewska I, Cylus JD, McDaid D, et al. Thematic Study: Cost analysis of health care provision for irregular migrants and EU citizens without insurance. 2016;(December).
160. Pottie K, Martin JP, Cornish S, Biorklund LM, Gayton I, Doerner F, et al. Access to healthcare for the most vulnerable migrants: a humanitarian crisis. Confl Health [Internet]. 2015;9(1):16. Available from: http://www.conflictandhealth.com/content/9/1/16
161. Gibson BA, Ghosh D, Morano JP, Altice FL. Accessibility and utilization patterns of a mobile medical clinic among vulnerable populations. Health Place [Internet]. 2014;28:153–66. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1353829214000665
162. Leiler A, Bjärtå A, Ekdahl J, Wasteson E. Mental health and quality of life among asylum seekers and refugees living in refugee housing facilities in Sweden. Soc Psychiatry Psychiatr Epidemiol [Internet]. 2019;54(5):543–51. Available from: http://dx.doi.org/10.1007/s00127-018-1651-6
163. Tinghög P, Malm A, Arwidson C, Sigvardsdotter E, Lundin A, Saboonchi F. Prevalence of mental ill health, traumas and postmigration stress among refugees from Syria resettled in Sweden after 2011: A population-based survey. BMJ Open. 2017;7(12).
164. Li SSY, Liddell BJ, Nickerson A. The Relationship Between Post-Migration Stress and Psychological Disorders in Refugees and Asylum Seekers. Curr Psychiatry Rep [Internet]. 2016;18(9):1–9. Available from: http://dx.doi.org/10.1007/s11920-016-0723-0
165. Andersson LMC, Hjern A, Ascher H. Undocumented adult migrants in Sweden: mental health and associated factors. BMC Public Health [Internet]. 2018;18(1):1369. Available from: https://doi.org/10.1186/s12889-018-6294-8
166. Craig GM, Daftary A, Engel N, O'Driscoll S, Ioannaki A. Tuberculosis stigma as a social determinant of health: a systematic mapping review of research in low incidence

countries. Int J Infect Dis [Internet]. 2017;56:90–100. Available from: http://dx.doi.org/10.1016/j.ijid.2016.10.011
167. Courtwright A, Turner AN. Tuberculosis and stigmatization: Pathways and interventions. Public Health Rep. 2010;125(SUPPL. 4):34–42.
168. Nkulu FK, Hurtig A-K, Ahlm C, Krantz I. Screening migrants for tuberculosis - a missed opportunity for improving knowledge and attitudes in high-risk groups: A cross-sectional study of Swedish-language students in Umeå, Sweden. BMC Public Health [Internet]. 2010;10(1):349. Available from: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-10-349
169. Sweetland AC, Galea J, Shin SS, Driver C, Dlodlo RA, Karpati A, et al. Integrating tuberculosis and mental health services: global receptivity of national tuberculosis program directors. Int J Tuberc lung Dis. 2019;23(5):600–5.
170. Kruijshaar ME, Lipman M, Essink-Bot M, Lozewicz S, Creer D, Dart S, et al. Health status of UK patients with active tuberculosis. Int J Tuberc Lung Dis. 2010;14(3):296–302.
171. Marra CA, Colley L, Moadebi S, Elwood RK, Fitzgerald JM. Health-Related Quality of Life Trajectories Among Adults With Tuberculosis *. Chest [Internet]. 2008;133(2):396–403. Available from: http://dx.doi.org/10.1378/chest.07-1494
172. Brazier J, Ratcliffe J, Salomon J, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation: Edition 2. Oxford University Press (maker); 2016.
173. Willige G Van De, Wiersma D, Nienhuis FJ, Jenner JA. Changes in quality of life in chronic psychiatric patients : A comparison between EuroQol (EQ-5D) and WHOQoL. Qual Life Res. 2005;(14):441–51.
174. Brazier J, Jones N, Kind P. Testing the Validity of the Euroqol and Comparing It with the SF-36 Health Survey Questionnaire. Qual Life Res. 1991;2(3):169–80.
175. García-Gordillo MÁ, Del Pozo-Cruz B, Adsuar JC, Cordero-Ferrera JM, Abellán-Perpiñán JM, Sánchez-Martínez FI. Validation and comparison of EQ-5D-3L and SF-6D instruments in a Spanish Parkinson´s disease population sample. Nutr Hosp. 2015;32(6):2808–21.
176. Selivanova A, Buskens E, Krabbe PFM, Ferreira LN, Ferreira PL, Ribeiro FP, et al. Comparing measurement properties of the EQ-5D-3L, ICECAP-O, and ASCOT in frail older adults. Value Heal [Internet]. 2015;9(1):715–25. Available from: http://dx.doi.org/10.1111/j.1524-4733.2006.00108.x
177. Arifin B, Purba FD, Herman H, Adam JMF, Atthobari J, Schuiling-Veninga CCM, et al. Comparing the EQ-5D-3 L and EQ-5D-5 L: studying measurement and scores in Indonesian type 2 diabetes mellitus patients. Health Qual Life Outcomes. 2020;18(1):1–9.
178. You R, Liu J, Yang Z, Pan C, Ma Q, Luo N. Comparing the performance of the EQ-5D-3 L and the EQ-5D-5 L in an elderly Chinese population. Health Qual Life Outcomes. 2020;18(1):1–7.
179. Eneqvist T, Nemes S, Kärrholm J, Burström K, Rolfson O. How do EQ-5D-3L and EQ-5D-5L compare in a Swedish total hip replacement population? Acta Orthop. 2020;91(3):272–8.
180. Wang P, Luo NES, Tai ES, Thumboo J. The EQ-5D-5L is More Discriminative Than the EQ-5D-3L in Patients with Diabetes in Singapore. Value Heal Reg Issues [Internet]. 2016;9:57–62. Available from: http://dx.doi.org/10.1016/j.vhri.2015.11.003
181. Hernandez Alava M, Wailoo A, Grimm S, Pudney S, Gomes M, Sadique Z, et al. EQ-5D-5L versus EQ-5D-3L: The Impact on Cost Effectiveness in the United Kingdom. Value Heal [Internet]. 2018;21(1):49–56. Available from:

http://dx.doi.org/10.1016/j.jval.2017.09.004
182. Mulhern B, Feng Y, Shah K, Janssen MF, Herdman M, van Hout B, et al. Comparing the UK EQ-5D-3L and English EQ-5D-5L Value Sets. Pharmacoeconomics [Internet]. 2018;36(6):699–713. Available from: https://doi.org/10.1007/s40273-018-0628-3
183. Kittikraisak W, Kingkaew P, Teerawattananon Y, Yothasamut J. Health Related Quality of Life among Patients with Tuberculosis and HIV in Thailand. 2012;7(1):6–13.
184. Haukaas FS, Arnesen TM, Winje BA, Aas E. Immigrant screening for latent tuberculosis in Norway: a cost-effectiveness analysis. Eur J Health Econ. 2016 Mar;
185. Wahedi K, Biddle L, Bozorgmehr K. Cost-effectiveness of targeted screening for active pulmonary tuberculosis among asylum-seekers. Eur J Public Health [Internet]. 2020;30(Supplement_5):1–19. Available from: http://dx.doi.org/10.1371/journal.pone.0241852
186. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent tuberculosis: A multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis [Internet]. 2011 Jun;11(6):435–44. Available from: http://dx.doi.org/10.1016/S1473-3099(11)70069-X
187. Aronsson M, Husberg M, Kalkan A, Eckard N, Alwin J. Differences between hypothetical and experience-based value sets for EQ-5D used in Sweden: Implications for decision makers. Scand J Public Health. 2015;43(8):848–54.